THE MILROY LECTURES

ON

EPIDEMIC DISEASE IN ENGLAND—THE EVIDENCE OF VARIABILITY AND OF PERSISTENCY OF TYPE.

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EPIDEMIC DISEASE IN ENGLAND—THE EVIDENCE OF VARIABILITY AND OF PERSISTENCY OF TYPE.

LECTURE I.[1]

MR. CENSOR AND GENTLEMEN,—Changes of type in epidemic diseases was the subject chosen by Dr. B. A. Whitelegge for the Milroy Lectures of 1893, to which the reader perforce returns again and again, as if increase of appetite had grown by what it fed on. The same topic has been variously approached, and in recent years more particularly from the evolutionary standpoint.[2] Already, towards the close of the seventeenth century, Sydenham had been accorded a Pisgah sight of the land to be explored, but prior to the Registrar-General and to Darwin no considerable advance into this new territory was possible. Even in the "'fifties" there was much speculation, which now seems strangely out of date. Murchison contended, on the one hand, for the *de novo* origin of typhoid fever, and he notes, "No mention is made of specific disease in the Mosaic account of the Creation, when we are told that every living creature and herb of the field was created, and it would be

[1] Delivered on March 1st.

[2] The *Transactions* of the Epidemiological Society contain Papers by Sir R. Thorne (1878), Dr. Hubert Airy (1878), Dr. Longstaff (1879-80), Dr. Ransome (1881-82), Dr. Franklin Parsons (1883-84), Dr. Louis Parkes (1890-91), Dr. G. Sims Woodhead (1890-91), and Dr. Herbert Durham (1899-1900). Sir Wm. Collins published his "Specificity and Evolution in Disease" in 1884, and an address, "The Man *versus* the Microbe," in 1902. The articles by Hueppe and Cartwright-Wood (*Lancet*, December 7th, 1889), and by T. W. Thompson (Stevenson and Murphy's *Hygiene*) may also be referred to. Finally, Creighton's translation of Hirsch and his *History of Epidemics in Britain*, and Hecker's *Epidemics of the Middle Ages*, have been largely drawn upon.

absurd to imagine that all of them have sprung from Adam." On the other hand, he observes that "although typhus varies in its severity and duration at different times and under different circumstances, there is no evidence of any change in type or essential characters. The typhus of modern times is the same as that described by Frascatorius and Cardanus."

The pages of the *Edinburgh Medical Journal*, 1856-58, contain a discussion on the transition from the "sthenic or phlogistic character" of continued fever in an earlier twelve years to the "asthenic or adynamic character" in the twelve years which had then just elapsed. Blood-letting, formerly widely practised, had been practically abandoned as a method of cure. In those days the generally-accepted doctrine was, as Dr. Stokes expressed it, in his second lecture on Fevers, that changes of type were to be recognised "chiefly by the therapeutical test, by the behaviour of disease, general or local, under treatment." Murchison argued, however—putting forward quite a novel view—that the supposed change of type was really a change from one kind of fever—relapsing fever—to another kind of fever, typhus. This, and not the practice of blood-letting, explained the lower mortality in the earlier period; the "diversity resided in the mental revolutions of practitioners rather than in the actual revolutions of disease." Murchison might, *à propos* of the errors he was combating, have quoted the passage cited by Dr. Milroy from John Locke: "Were the imperfections of language as the instrument of knowledge more thoroughly weighed, a great many of the controversies that make such a noise in the world would of themselves cease, and the way to knowledge, and to peace, too, lie a great deal opener than it does;" while to the same effect Bacon has remarked—"Although we think we govern our words, yet certain it is that words, as a Tartar's bow, do shoot back upon the understanding of the wisest, and mightily entangle and pervert the judgment."

The Registration Act of 1837, as has often been observed, marks a new departure. Dr. Farr commented upon the notable advance made when statistical records were first applied to the study of epidemic disease. The Registrar-General calculates rates to two places of decimals, but there is still no precise agreement as to the nature of the units dealt with. Is "typhus," for example, the disease of 1847, or that which smouldered in Bermondsey in 1903? Scarlet fever is said to prevail nowadays in an attenuated form,

but there is no scale by which to gauge it. The child reaches a stage in his mental development when he begins to wonder why he has been content to accept some concrete piece of string or chalk as a test object to be referred to in discussing questions of length or size. The units referred to by the epidemiologist are, unfortunately, still of this primitive character; there is no standard case of typhus fever deposited at Kew, and no one proposes to test strains of small-pox by their ability to kill unvaccinated vagrants of given weights in specified times.

Murchison has remarked that "in distinguishing the different forms of continued fever, too much reliance has been placed on their symptoms and pathology, while there has been a want of sufficient investigation of their causes." With elaboration of the germ theory, the pendulum has swung to the other extreme, and it is now quite orthodox doctrine to hold that the presence of a particular germ spells specific disease; indeed, it may be questioned whether some modern bacteriologists, in the light of the demonstration of diphtheria, cholera, and enteric fever bacilli in persons presenting no symptoms of illness, would not feel that Murchison much exaggerated the difficulties inherent in an hypothesis requiring the co-existence of all pathogenic organisms in one individual. "The germ," Sir William Collins says, "has, perhaps, been too much with us, and the paramount importance of soil has been absurdly underrated." Again, to quote Dr. G. Newman, "The early school of preventive medicine declared for the health of the individual, and laid the emphasis upon predisposition; the modern school have declared for the infecting agent, and have laid emphasis upon the bacillus. The truth is to be found in a right perception of the action and interaction of the tissues and the bacillus." Or, as Dr. F. G. Clemow expresses it, "Though constantly spoken of as if it were a material tangible entity, disease is, in fact, no such thing. It is only a morbid phenomenon, or rather a group of morbid processes, in the tissues of a particular animal organism. In the language of logic, it is not even a phenomenon, but an epiphenomenon."

Here is a fertile source of difficulty and misapprehension. It has been suggested that rhythmical evolutionary changes in the life-history of micro-organisms may prove explanatory of waves of disease, but is the rhythm manifested in the micro-organism or in that epiphenomenon the interaction between germ and tissues? If the latter, we dispose

at once of a difficulty. The fossils in the strata do not recur cyclically, a species once extinguished never reappears. Is this true also in the case of disease germs, or must these "lowly organisms, on the borderland of the animal and vegetable kingdoms, on the threshold, as it were, of the organic and inorganic, . . . whose cycle may be less than an hour, and whose rate of propagation is incalculable" (Collins), be regarded as exceptional? Sir George Darwin has discussed "the extent to which ideas parallel to those which have done so much towards elucidating the problems of life hold good also in the world of matter." He regards the several chemical elements as "different kinds of communities of corpuscles which have proved by their stability to be successful in the struggle for life." Again, he says: "An atom continuously radiates and loses energy, and must ultimately run down as a clock does. Its decay may be very slow, it may run for 1,000,000 years, but it cannot be eternal." From this new point of view, the older ideas concerning evolution come under criticism.[1]

It might be thought that study of the records of disease would throw light upon change of type. Indeed, Sydenham hints as much, but expresses the view that the materials which could be collected in a single lifetime would not be abundant enough for the purpose. Hecker points out, moreover, that "such an insight into disease as is worthy of the dignity of a science cannot be obtained by observation of isolated epidemics, because Nature never in any one of them displays herself in all her bearings nor brings into action at one time more than a few of the laws of general disease. One generation, however rich it may be in stores of im-

[1] Thus Sir George Darwin expresses a doubt "whether biologists have been correct in looking for continuous transformation of species." "Judging by analogy, we should rather expect to find slight continuous changes occurring during a long period of time followed by a somewhat sudden transformation into a new species or by rapid extinction," and he proceeds to refer to "Theories of physical evolution which involve the discovery of modes of motion or configurations of matter which are capable of persistence. The physicist describes such types as stable; the biologist calls them species." Again, Weismann writes, "The idea of species is fully justified in a certain sense. We find, indeed, at certain times a breaking-up of the fixed specific type, the species becomes variable, but soon the medley of forms clears up again, and a new constant form arises—a new species which remains the same for a long series of generations until ultimately it too begins to waver, and is transformed once more." Bastian finds in the persistence of low types of life evidence of the "continual surging up through all geologic time of freshly-evolved forms."

portant knowledge, is never adequate to establish, on the foundation of actually-observed phenomena, a doctrine of diseases worthy of the name."

In the first instance, it is necessary to lay down a *scale* indicating the rate at which forms of life may be presumed to vary. On the one hand there is evidence of extraordinary persistency of type. "What is more certain," says Weismann, "than that the animals and plants around us remain the same as long as we can observe them, not through the lifetime of an individual only, but through centuries, and in the case of many species, for several thousand years. Certain genera of echinoderms, such as starfish (Astropecten), lived in the Silurian times, and they are represented nowadays in our seas by a number of species; and in the same way the cephalopod genus Nautilus has maintained itself among the living all through the enormous period from the Silurian sea to our own day. Similarly, the genus Lingula of the nearly extinct class of brachiopods has been preserved from the grey dawn of primitive times, with its records in the oldest deposits, and is represented in the living world of to-day by the so-called 'barnacle goose' mussel, Lingula anatina."

Huxley was fond of insisting upon the existence of what he called "persistent" types, and as long ago as 1862 he argued in a strain which shows that some of the doctrines enunciated by Sir George Darwin and Weismann were already accepted by him. He says that study of the positive facts of palæontology impresses us not with the greatness of the changes which are exhibited to view, but with the "smallness of the total change." Thus, "there are 200 known orders of plants; of these not one is certainly known to exist exclusively in the fossil state. The whole lapse of geological time has as yet yielded not a single new ordinal type of vegetable structure." The change in the animal world, though greater, is still singularly small. "No fossil animal is so distinct from those now living as to require to be arranged even in a separate class from those which contain existing forms. It is only when we come to the orders, which may be roughly estimated at about 130, that we meet with fossil animals so distinct from those now living as to require orders for themselves, and these do not amount, on the most liberal estimate, to more than about ten per cent. of the whole." Again, he refers to a lecture "On the Persistent Types of Animal Life," delivered in 1859, in which

it was stated "that there are carboniferous plants which appear to be generally identical with some now living; that the cone of the oolitic Araucaria is hardly distinguishable from that of an existing species; that a true Pinus appears in the Purbecks and a Juglans in the chalk; while from the Bagshot sands a Banksia, the wood of which is not distinguishable from that of species now living in Australia, had been obtained."[1]

But, on the other hand there may be rapid transformation under conditions favourable to change; and here the phenomena of variation under domestication, and the behaviour of species under conditions of isolation, must more particularly be referred to. Darwin made his careful study of domesticated animals and of cultivated plants because he considered it to "afford the best chance of making out" the "obscure problem." He traced the 150 and more subbreeds of dog to some seven or eight extinct canine species. He writes: "Compare the racehorse, drayhorse, and a Shetland pony in size, configuration, and disposition, we see greater differences than exist between the seven or eight other living species of the genus Equus."

Upon the case of the pigeon he especially laid stress, tracing all the varieties of domestic pigeon, which he classed in four groups including some 150 kinds, to one source, the rock pigeon, Columbia livia; yet he says, "several of the most strongly-characterised domestic forms, if found wild, would have been placed in at least five new genera. . . . Anyone now visiting a well-stocked English aviary would certainly pick out the jacobin, turbit, pouter, etc., as distinct kinds. If the same person could have viewed the pigeons kept, before 1600, by Akbar Khan in

[1] The same authority notes the resemblance of the Silurian tabulate corals to those which now exist; while, he says, eleven existing genera of Mollusca "are given without a doubt as Silurian in the last edition of *Siluria*, and one of the highest cephalopod forms of the lias (Belemnoteuthis) presents the closest relation to the existing Loligo." Examples are cited, too, from higher forms. "Among fish, the carboniferous Pleuracanthus differs no more from existing sharks than these do from one another." The Ganoid fossils, despite their great range in time are referable to existing subordinal groups. The Beryx of the chalk (among Teleostean fishes) is represented by closely-allied living species in the Atlantic and Pacific Oceans. Among reptiles the highest living group—that of the Crocodilia—is represented at the early part of the Mesozoic epoch by species almost identical. Even among mammals the scanty remains tell the same story. In a later lecture (American Addresses, Lecture II), Huxley returned to this theme.

India and by Aldrovandi in Europe, he would have seen the jacobin with a less perfect hood; the turbit apparently without its frill; the pouter with shorter legs, and in every way less remarkable—that is, if Aldrovandi's pouter resembled the old German kind; the fantail would have been far less singular in appearance, and would have had much less feathers in its tail; he would have seen excellent flying tumblers, but he would in vain have looked for the marvellous short-faced breed; he would have seen birds allied to barbs; and, lastly, he would have found carriers with beaks and wattle incomparably less developed than in our English carriers." Even pigeon fanciers, says Darwin, who believe the chief races to be descended from distinct aboriginal stocks, yet admit "that the so-called toy-pigeons (spots, nuns, helmets, etc.), which differ from the rock pigeon in little except colour, are descended from this bird. . . . It would, indeed, be as puerile to suppose them descended from as many wild stocks as to hold this to be the case with the many varieties of the gooseberry, heartsease, and dahlia." Specially noteworthy in connection with variation in the pigeon is the dictum of Sir John Sebright, quoted by Darwin, to the effect that "he would produce any given feather in three years, but it would take him six to obtain head and beak."

Turning now to the phenomena exhibited under conditions of isolation, there is particularly striking evidence of the fact that, as Weismann puts it, "the conditions of life are, so to speak, the mould into which natural selection is ever pouring the species anew." Insular regions harbour "so-called endemic species, that is to say, species which occur nowhere else upon the earth," and they are the more numerous the further the island is removed from the nearest area of related species. Thus the Sandwich Islands, which originated as volcanoes in the midst of the Pacific Ocean more than 4,000 kilometres from the continent of America, possess "eighteen endemic land birds, and no fewer than 400 endemic terrestrial snails." The Galapagos Islands, 1,000 kilometres from the coast of South America, yield "twenty-one endemic species of land birds . . . (including) about a dozen different, but nearly related, mocking-birds, each of which is found in only one or two of the fifteen islands." The endemic birds in such island groups differ solely or mainly in their colouring, and the differences are, generally speaking, specially marked in the males. This is also the case in the humming-birds, about

150 species of which occur in the tropics of the New World, species having often "quite a small area of distribution, many are restricted to a single volcanic mountain, living in the forests which clothe its sides . . . presumably because they cannot endure the climate of plains. In the light of the *rôle* played by isolation in higher forms, it may be that the importance to be attached to the behaviour of bacteria in pure cultures should be properly deemed to call for some further consideration.

It is quite clear that in instituting comparisons between the behaviour of diseases and the more or less gradual evolution of specific types in animals and plants, due regard must be paid to various considerations. The organisms associated with disease are simple and lowly organisms; their transmutations may be more rapid than those of more complicated forms. According to Sir George Darwin, "the time needed for a change of type in atoms and molecules may be measured by millionths of a second, while in the history of the stars continuous changes occupy millions of years. Notwithstanding this gigantic contrast in speed, yet the process involved seems to be essentially the same." Weismann writes: "In a certain sense we may say that simpler, more lowly organisms are more capable of adaptation than those which are highly differentiated and adapted to specialised conditions in all parts of their bodies, since from the former much that is new may arise in the course of time, while very little and nothing very novel can spring from the latter." On the other hand, it has been pointed out by Darwin that "a very simple form fitted for very simple conditions of life might remain for indefinite ages unaltered or unimproved; for," he says, "what would it profit an infusorial animalcule, for instance, or an intestinal worm to become highly organised?"

It may be noted further that but little is known concerning the reproduction of disease organisms, and the question of the occurrence or non-occurrence of amphimixis may be of importance. There is no sexual reproduction so far as has been ascertained in schizomycetes and saccharomycetes, though it has again and again been surmised that the bacteria may be but phases in the life-history of higher forms; in the protozoa, on the other hand, sexual reproduction occurs. Weismann refers to algæ of the genus Laminaria, which is said to multiply only through asexual swarm spores, and he says "there seems nothing against the assumption that these tangles have existed for a long

time under uniform conditions and have become adapted to them with a high degree of constancy." Again, he alludes to the lichens, which represent a life partnership between fungi and algæ, and in which amphimixis appears not to occur at all. These algæ can also live independently, and the same species of alga may combine with several different fungi to form different species of lichen, just as the same fungus may also form part of several species of lichen. He concludes that "lichens formerly possessed a sexual reproduction, but that they have lost it, though whether all have done so is perhaps not yet quite certain. The same assumption," he continues, "must be made in regard to the basidiomycetes among the fungi, and for most of the ascomycetes, for in these groups of fungi sexual reproduction has only been demonstrated with certainty in a few genera. Whether," he adds, "it may be assumed that the fungi which are now asexual are no longer capable of new adaptations, and whether their parasitic habit may be regarded as making up in some way for the lack of the remingling of the germplasm, as the botanist Möbius supposes, I am not able to decide. It is obvious that data in regard to amphimixis among the fungi are still incomplete, and recent investigations lead us to suspect that sexual mingling may not be absent but only disguised." At the present time, then, nothing certain can be said as to the influence exerted by amphimixis, though the suggestion of Möbius raises the question whether we are concerned not merely with the evolution of a particular species but with the interaction between species and species. The fact that disease is an epiphenomenon again confronts us.

On a review, then, of the changes of type exhibited by the higher forms of life marked contrasts are presented—on the one hand extreme stability, as in Lingula; on the other, variability, as in the pigeon or the humming bird. But even in higher forms—and the difficulty is far more serious in dealing with bacteria—how much depends upon the characters held to determine specific differences. The shepherd distinguishes one sheep from another; Darwin quotes Mr. Dixon as affirming that "to every hen belongs an individual peculiarity in the form, colour, and size of her egg, which never changes during her lifetime, so long as she remains in health, and which is as well known to those who are in the habit of taking her produce as the handwriting of their nearest acquaintance." It is but a step to the modifications in plumage which in the humming-

bird connote specific differences, and, as we have seen, varieties of domesticated pigeon stand as far apart one from another as do actual genera of Columbidæ living under natural conditions. Enough has been said to show how great are the difficulties which hedge about any attempt to estimate, *a priori*, the rate at which the evolution of disease germs proceeds.

It would appear at first sight, perhaps, in turning to epidemiological records for information as regards persistency or variability of type that we are engaging in a hopeless quest. Darwin wrote: 'I look at the natural geological record as a history of the world imperfectly kept and written in a changing dialect; of this history we possess the last volume alone relating only to two or three countries. Of this volume only here and there a short chapter has been preserved, and of each page only here and there a few lines." But the difficulties of the geological record are as nothing compared with those which now confront us, for an epidemic disease leaves "no bones behind it in the strata."

On passing backwards two-thirds of a century the loss of death-statistics for the whole country is an almost overwhelming one; the London bills of mortality still stretch away for a brief space into the early part of the seventeenth century, telling of small-pox, measles, whooping-cough, in a very unsatisfying manner of the group of fevers, and in the earlier years of plague. In the pages of Huxham, Fothergill, and others, the behaviour of throat malady is more or less imperfectly traceable as far as the early part of the eighteenth century. There are the materials for carrying the history of influenza at least a hundred years further still. But as we proceed backward difficulties augment, charts fail, the lights are only dimly discernible, though that of Sydenham shines far away in the seventeenth century; plague is still there, stretches back, indeed, from 1666 to the middle of the fourteenth century and maybe beyond; mysterious shapes, the 'sweating sicknesses" of the late fifteenth and early sixteenth centuries, and shortly prior to that time the "garrotillo" of Spain loom out of darkness; there is the strange epidemic extension of lues venerea and more remote still the ergotism of the rye-eating populations of the continent, the "leprosy" of the Middle Ages, stray allusions to deadly outbreaks within the walls of monasteries, and then still earlier the famines and murrains which are all that remain until

we ultimately reach "Beda's plague" in the seventh century of our era. Thus rapidly we pass to the "primordial field of physical evil" of which Sir John Simon has spoken in the opening paragraphs of his *English Sanitary Institutions.*

In looking for enlightenment upon the question of change of type a mass of material presents itself for study. Sir James Paget raised doubt as to whether any result of value would accrue from pursuing the historical method; Hecker is more sanguine. "The diseases of nations," says he, "constitute an immeasurable and unexplored country. Small is the number of those who have traversed it; often have they arrested their steps filled with admiration at striking phenomena; have beheld inexhaustible mines waiting only for the hand of the labourer and from contemplating the phenomena of collective organic life, which science nowhere else displays to them on so magnificent a scale, have experienced the sacred joy of the naturalist to whom a higher source of knowledge has been opened."

Little can be made of the early pestilences, murrains, and famines. In this country especially famine seems to have continually recurred; indeed, there is an old saying particularly identifying England with famine, and at the same time ascribing St. Anthony's fire to France and leprosy to Normandy. The mediæval "leprosy," again, is a veritable will-o'-the-wisp. Creighton considers in some detail the extraordinary confusion of ideas introduced by religious sentiment into conceptions concerning the leper and the lazar house, and ultimately arrives at the conclusion that in mediæval England the village leper was about as common as the village fool.[1]

The epidemic disease which first appears in unmistakeable guise upon the stage of English history is plague. The Black Death was described by Guido de Cauliaco as presenting at Avignon two different fashions, one attended with "spitting of blood" and the other with "boils and sloughs in the external parts." Hirsch propounded the theory that the Black Death came from India, inasmuch as

[1] It has been suggested that prevalence of leprosy stood in relationship to the use of salted fish. There is a famous passage in White's *Selborne* bearing on this which is quoted by Creighton, who further notes it as being significant, having in view the prevalence of leprosy in Norway for centuries, that William of Malmesbury, referring to those who went to the First Crusade, says "Scotus familiaritatem pulicum reliquit, Noricus cruditatem piscium." The thesis has in recent years found an ardent exponent in Mr. Jonathan Hutchinson.

it conformed to what he described as the "Indian type," being frequently complicated with bleeding from the lungs. Later experience does not support a thesis of the existence of distinct Levantine and Indian types of plague, and pneumonic plague appears to be much more widely distributed than it was formerly supposed to be. Mr. E. H. Hankin[1] contends, however, that there are certain resemblances between the Black Death and all the known plagues of Western India, and he suggests that they had a common origin, and that Gahrwali fakirs journeying to a religious festival, held at twelve yearly intervals at Nassik, were the infecting agents. Did time permit, it would be interesting to pursue this question of differing types of plague: and further to refer to the settling down of the disease in the English towns; to the great exacerbations of plague from time to time in the fifteenth and sixteenth centuries; to the repeated mention made of coincident infection of animals; to the explosions of the seventeenth century and to Creighton's assignation of the altered behaviour of the disease to changing practices in relation to burial; to the great plague of 1665-66; and then, finally, to the disappearance of the disease from England and (save for a localised prevalence at Marseilles in 1720) from Europe until our own day.

It must suffice, however, to point out that on a comprehensive survey of the records of the disease in the light of existing knowledge, it appears there is justification for holding, with Murchison, that diversity has resided in the mental revolutions of practitioners rather than in the actual revolutions of disease. It may be difficult to explain the prominence given to carbuncles and "tokens" in one age or to hæmorrhage from the lungs in another; but the evidence demonstrates the operation century after century of a disease entity which has presented a strange capacity for calling forth, at long distant periods and in remote climes descriptions bearing a striking resemblance despite the diverse circumstances under which they have been written.

But passing from plague we are confronted with a most disturbing phenomenon from the point of view of those who seek to establish "a doctrine of popular diseases worthy of the name." The account generally given of the English sweat, *sudor Anglicus*, "that mist-born spectre,"

[1] *Journal of Hygiene*, January, 1905.

as Hecker terms it, is that the disease suddenly appeared upon the stage of history in 1485, recurred in 1508, 1517, and 1528, and yet a fifth time in 1551, and then disappeared never to return. Creighton observes that "writers on the English sweat, hitherto, have had to depend on the somewhat meagre and not always consistent statements of annalists, for their knowledge of its first authentic occurrence"; he adds that he is able to adduce the evidence furnished by a manuscript written by a contemporary physician. Even with this additional source of information available the records of the English sweat strikingly illustrate the fragmentary character of the materials from which history has to be built up and show how statements, to which originally little or no value was presumably attached, by being copied by writer after writer, have gradually come to be invested with an appearance of authority. The only contemporary record (Polydore Virgil's account "was certainly not begun until after 1504 and was not published until 1531") which gives details of the first sweating sickness is, then, the MSS. of a Dr. Thomas Forrestier, a native of Normandy, tarrying in London in 1485, and apparently encountering difficulties there two years later, when he was granted "pardon for all escapes and evasions out of the Tower of London and elsewhere, and remissions for forfeiture of all lands and goods." This authority describes the new disease as coming "with a grete swetying and stynkyng, with rednesse of the face and of all the body, and a contynual thurst, with a grete hete and headache because of the fumes and venoms." He fixes the date of commencement of the outbreak in London as September 19th, 1485.

Practically all that is known of the second, third, and fourth sweats in England, comes originally from the annals of the historian and poet laureate, Bernard André, from the history of the Italian scholar and "man of affairs," Polydore Virgil, and from an occasional chance reference in State papers, such, for example, as that furnished in an ambassadorial despatch when the Venetian envoy asks his Government, in 1517, to replace him, as he wishes to escape from "sedition, sweat, and plague."[1] The fifth sweat, in

[1] Creighton notes that in the *History of Cork*, by C. Smith, M.D., there is an entry, under 1528, concerning "a malignant disorder called the Sweating Sickness in Cork," and adds, "It has been generally supposed that the sweat did not enter Ireland or Scotland in any of its five outbreaks." Du Bellay, the French Ambassador, refers

1551, for the first time, says Creighton, "called forth two native writings, one for popular use in English, in 1552, and another in Latin, in 1555, both by Dr. Kaye, or Caius, physician to Henry VIII and Edward VI," and for seven years president of this College. Apart from him, there are references to the outbreak in the diaries of a London citizen, Machyn, and of Edward VI. The dearth of contemporary medical treatises on the English sweat is truly remarkable, and in particular the absolute silence of Linacre on the subject has been commented upon by Hecker among others.

The "Boke or Counseill against the disease commonly called the Sweate or Sweatyng Sicknesse," made by Jhon. Caius throws more light upon the state of medical learning of the time than upon the "Sweatyng Sicknesse." The author says the disease was named in other countries the English sweat, because it "firste beganne in Englande;" but he notes that "some conjecture that it or the like hath bene before seene among the Grekes in the siege of Troie, in th ēperor Octavius warres at Cantabria, called now Biscaie, in Hispanie and in the Turkes at the Rhodes." In a later passage, in speaking of Troie, he mentions the fact that "dogges and mules were first attacked there and after men in great numbre," but he does not specifically state that dogges and mules were attacked in 1551. He calls the disease Ephemera, having in his mind no doubt "the Ephemera that Galene writeth of," and he cites Galen as authority for his doctrine that "our bodies canot suffer any thīg or hurt by corrupt and infective causes, except ther be in thē a certie mater prepared apt and like to receive it, els, if one were sick all should be sick, if in this countrie in al coūtries, when the infection came, which thīg we se doth not chāce."

Then follows an enunciation of the extraordinary doctrine that the disease attacked only English people. In "Cales, Antwerpe, and other places of Brabant, only our countrimen ware sicke and none others except one or two others of thenglishe diete which is also to be noted." Apart from any other considerations, the contemporary chroniclers themselves are by no means in agreement as to this

more than once to the sweat in 1528; Henry VIII discusses the subject with Anne Boleyn, and he advises Wolsey to use the pills of Rhazes once a week, and flies himself from place to place until he reaches Tyttenhanger, where he elects to "take his chance of the sweat, keeping up immense fires to destroy the infection."

supposed law; passing over the conjectures as to the outbreak at Troy, in 1517, we note that Ammonius of Lucca was "cut off in the flower of his age;" again, the Venetian Ambassador suffered at least from apprehensions, and in 1529 the English sweat admittedly spread far and wide on the Continent. The notion that particular nationalities, etc., were immune, or the reverse, may be compared with that entertained at Lubeck in 1529, when the English sweating fever was held to be "a punishment which heaven inflicted on the Martineans, for so they called the followers of Luther, and the people were not undeceived until they saw with astonishment that Catholics also fell sick and died" (Hecker).

Caius says: "The fifth Ephemera of Englande began at Shrewsbury," and Hecker has constructed a picture of the disastrous progress of the disease "along the valley of the Severn," prior to its proceeding to London. Meagre as are the other contemporary sources of information, this precise geographical location of the outbreak must unquestionably be challenged. Thus Creighton cites the parish register of Loughborough, June, 1551, where an entry appears concerning "the swet called new acquaintance, alias stoupe knave and know thy master;" and again, from Dorset, a reference to "the posting sweat, that posted from town to town thorow England, and was named 'stop gallant,' for it spared none;" and one to "the hote sickness or stop gallant," from Devonshire; one to a great plague at York; and one to two deaths in Huntingdonshire. Caius says the east and north were attacked, and no doubt Creighton's statement that it was "diffused all over England in the manner of influenza" may be accepted. The fourth sweat (1528) is said to have invaded the Continent in 1529, avoiding France, not entering Spain, and not crossing the Alps, but extending over the rest of Europe, "in much the same way," says Creighton, "as if it had been an influenza reversing the order of its usual direction." In Germany, several pamphlets on the new malady appeared, of which Hecker gives account.[1]

[1] They show, as Creighton observes, "an enormous range" of fatality, and furnish interesting particulars as to therapeutical methods. Thus the patients were placed, "whether they had the sweating sickness or not (for who had calmness enough to distinguish it), instantly to bed," covered with clothes, windows being closed until the patient, as the old writer says, "finally in this rehearsal of hell being bathed in an agonising sweat gave up the ghost." Another writer complains

Enough has been said to show how far we are from possessing a satisfactory description by contemporary writers of the supposed new disease; indeed, so far as the four earlier outbreaks are concerned, the particulars to hand in this country may be compared with the sort of information it might be possible to glean, say, concerning the influenza of 1803, from fragments of the correspondence of the Poet Laureate and the Italian Ambassador of the time. Much is capable of explanation, if once it is decided not to treat the contemporary records more seriously than they deserve. Is it not mysterious that when, ceasing to be peculiarly English, the sweat overran the Continent it did not affect France? While the year 1551, that of the last sweat, "curiously coincided," says Creighton, "with influenza (coqueluche) in France." Strangest of all, "during the prevalence of influenza in Britain in 1510, Spain was afflicted with sweating sickness" (Villalba). The accepted account of five clean-cut English epidemics is almost certainly misleading. The Graf von Newenar, Provost of Cologne, maintained, indeed, that sweat broke out in England every year, but this Hecker considers "unworthy of credence." In 1511 (not a "sweat" year), Erasmus complains of his health being rather doubtful "from that sweat" (*a sudore illo*). This may, as Creighton says, "possibly refer to the lingering effects of an attack in 1508 or to the influenza of 1510." Again, there were "hot agues" in England in 1518 and 1540. The conditions, so far as importation of infection is concerned, were very different in the sixteenth from those in the nineteenth century, a point to which I propose to revert later, but it is conceivable that in some such way as the influenzas of 1803, 1833, 1837, 1847-48, and 1890, stand out in the history of the nineteenth century, so the five sweats of the fifteenth and sixteenth centuries may merely represent marked exacerbations of a more or less established disease.

May we not go a step further, and question Polydore Virgil's dictum, "man of affairs" though he was, that the sweat was "a new kind of disease from which no former age had suffered, as all agree." Influenza in later times was over and over again the "new disease," or the "new acquaintance;" and certain it is that, as a literature of

of "ignorant interlopers who with their pills and their hellish electuaries flit about from place to place, especially where rich merchants were to be found, from whom, should they be restored, they obtain the promise of mines of gold."

Year.	References made to the English Sweating Sickness.		Re
1480	...	...	Encep nan
1481			(the Fri
1482	...	..	Febri Epide
1483	...	...	
1484	...	...	Malig nat
1485	In the beginning of August: Eruption of the English sweating sickness.		dea
1486	...	...	
1487			
1488	...	...	
1489	...	...	
1490	...	...	
1491			
1492			
1493			
1494			
1495	...	...	
1496			
1497			
1498			

e cerebritis was an inflammatory fever, with delirium and intense head-
:he higher classes were frequently attacked. It was, perhaps, says Hecker,
:al with the fever which at the same period desolated the north-west
many as far as the shores of the North Sea.

sweating sickness gradually emerges to view, it and influenza are inextricably confused. The clinical pictures of the two maladies do not exhibit marked differences, and we shall see immediately that outbreaks, variously designated but presenting clinically broad general resemblances, prevailed contemporaneously with the "English sweat" and with the strangely localised sixteenth-century "influenzas." From an epidemiological point of view, the diseases are very hard to distinguish.[1]

I have dissected out the *Chronological Survey*, prepared by Hecker, using his words and adding certain supplementary observations, for the most part derived from the text of his book on *Epidemics in the Middle Ages* (*vide* Table). The Table thus prepared strikingly illustrates the way in which, during the close of the fifteenth and the first half of the sixteenth centuries, England, France, Germany, Italy, Portugal, Spain, Holland, Norway, Sweden, Denmark, Russia, etc., are now involved in widespread prevalences of epidemic disease, now escape. It will be seen that the first sweat was preceded by "hauptkrankheit" in Westphalia, Hesse, and Friesland, "epidemic pleuritis" in Italy, and "febrile cerebritis" in France, and was contemporaneous with "malignant fever" in Germany and "plague" in Spain. The descriptions to hand relating to "hauptkrankheit," "epidemic pleuritis," and "febrile cerebritis," may profitably be compared with what we know concerning the English sweat and influenza respec-

[1] It may be urged that English sweat was more deadly than influenza. In the absence of case-mortality figures, certain loose statements have gained strength as they have travelled—for example, Holinshed's "scarce one amongst a hundred that sickened did escape with his life," or the Venetian Ambassador's "5000 deaths in three days" in the sweat of 1551. The deaths of two successive Lord Mayors and four Aldermen in 1485 could no doubt be matched with examples from our own day; but fortunately the question can be carried a stage further, for we have (Creighton, vol. i, 261) independent statements purporting to give the actual number of deaths in London in the prevalence of 1551. Eight or nine hundred deaths in a population of 120,000 is not out of all proportion to the mortalities which probably occurred in 1833 and 1837. Even in 1848 the deaths were about 1 in 1000, though in the big London outbreaks of recent years, those recorded as directly due to influenza have not exceeded 1 in 2,000. Creighton shows that opinion as to the fatal character of the disease was divided in 1528, quoting Henry VIII's reassuring statements to Anne Boleyn, "none of our Court and few elsewhere have died of it;" also the sceptical view of Brian Tuke—he concludes, "so far as mere numbers went, all the five London epidemics together could not have caused so great a mortality as the plague caused in a single year of Henry VII."

repeat itself so far as that matter is concerned. Creighton, in recording such particulars, says: "It would not be correct to say that these new fevers or influenzas, with more or less of the sweating type, were the sweat somewhat modified. But they seem to come in succession to the sweat, if not to have taken its place or supplanted it." And what, it might be asked, is to be said of the trousse galants, hauptkrankheits, and the rest, did the new fevers and influenzas succeed them? The historian of epidemics in this Tudor period, if he cling to the individuality of English sweat, cannot, indeed, refrain from holding that the similar forms of disease contemporaneously prevailing in the several continental countries were also each one of them individual and distinct; such a position is untenable. Creighton develops a "theory of the English sweat" which leads him to consider the connection between sudor Anglicus and the Picardy sweat. To this question it will be necessary to return, but before doing so it will be well to refer to the history of influenza.

LECTURE II.[1]

MR. PRESIDENT AND GENTLEMEN: Creighton gives the earliest clear reference to influenza in these islands at 1173, when there was an evil and unheard-of cough (*tussis mala et inaudita*) at Melrose, while in the same year a certain dean of St. Paul's, travelling on the Continent, found the whole world "infected by a nebulous corruption of the air, causing catarrh of the stomach and a general cough."[2]

There can be no room for doubt as to the character of the coqueluche[3] of 1510, whatever be thought of the five "sweats" already discussed, or of agues (such as the "hot agues of 1540") occurring during the first half of the sixteenth century. In 1557-58 occurred the epidemic which Dr. John Jones (*Dyall of Agues*) compared to the true sweat of 1551. It was "a new burning ague," and "one-third part of the population taste the general sickness." In 1562, there was an outbreak of the "new acquaintance;" Mary Queen of Scots was attacked by it in Edinburgh in this year. In 1580 the "gentle correction" appeared, and in 1596-98 there was prevalence of a malady which was, in all probability, influenza. Fuller describes the "ague" of 1558 as "a dainty-mouthed disease, which passing by poor people fed generally on principal persons of greatest wealth and estate;" and, indeed, "ague," which, as Creighton notes, means in early English merely a sharp fever, may now be said to have replaced the formerly fashionable "sweat."

"Influenza" seems to have been first applied to an epidemic in Italy, in 1729; at any rate, it is introduced in an account of that outbreak given in a London periodical in

[1] Delivered on March 6th.

[2] Some suspicion attaches, Creighton thinks, to a "rheumy infirmity" at St. Albans in 1427 and to the "pestilentia volatilis" recorded by Fordoun in Scotland in 1430 and 1432.

[3] Or coccolucio, so called because the sick wore a cap or covering over their heads. It raged all over Europe, "not missing a family, and scarce a person." It was marked by "a grievous pain of the head" . . . and "in some it went off by a looseness, in others by sweating" (Dr. Thomas Short, London, 1749).

1830. The word first appeared in England in 1743, but did not come into common use until the beginning of the nineteenth century. In the seventeenth century influenza was, says Creighton, variously designated "new disease," "new ague," "strange fever," "new delight," "jolly rant," "great cold," "unusual cold," "unusual transient fever," etc.; in the eighteenth century the expression "catarrh" was applied to it. As Robert Boyle notes: "The term 'new disease' is much abused by the vulgar, who are wont to give that title to almost every fever that, in autumn, especially varies a little in its symptoms or other circumstances from the fever of the foregoing year or season."

Catarrh is said to have prevailed throughout Europe in 1610; there was a "new disease" in 1612-13, and also in 1623-24; a "harvest ague" in 1625; a "new disease" in 1638-39, which was accompanied by a "harvest ague;" and a "new disease" again in 1643-44 and in 1651. In 1657-59, one, or possibly two, catarrhal epidemics prevailed, forming part of an outbreak of "new disease." In 1675 there was a universal cold. Evelyn notes (October 15th): "I got an extreme cold such as was afterwards so epidemical as not only to afflict us in this island but was rife over all Europe like a plague." Sydenham gives a chapter to the "epidemic coughs of the year 1675, with pleurisies and pneumonias supervening." The "severe and violent cough" of 1675 was known in the North of England "profanely" by the name "jolly rant." The winter outbreak of 1679 stands out particularly clearly in contemporary records. Sydenham says that 1678-80 were years of "epidemic agues," or "new disease." The agues were tertians or quotidians, or duplex forms of these: after two or three intermissions they were apt to become continual fevers. Moreover, at this time a morbus epidemicus, or febris epidemica, was prevailing in Holland and Belgium.

A noteworthy feature in influenza is the frequent coincident affection of animals. The universal sickness of the Siege of Troy has been held to have been influenza, because it began upon the horses and dogs. A London letter of 1658 states: "There is a great dearth of coach horses almost in every place, and it is come into our fields." Again, the characteristic rise of mortality in London in 1688, with its accompanying "new disease," was preceded by a slight but universal horse-cold, and numerous similar occurrences are recorded in the following century.

An account of "the short sort of fever" of 1688 comes

from Dublin. Patients experienced "a deep pain in their heads chiefly about the eyes, with unsettled pains in their limbs and about the small of their back, a soreness all over their flesh." Mention is also made of sweating. Such references occur again and again. Willis noted that the epidemic of 1658 was "wont to be cured within a few days by sweat." There was a universal cold in 1693, which "terminated in a critical diaphoresis" (Molyneux). Short, too, speaks of "the sweat" which was "the general crisis" of the disease, and alludes to sweating in the outbreak of 1710. In that year and in 1713 there is mention of the "Dunkirk rant," brought over in 1713, according to Mead, by troops returning from the Continent: a mild fever with pains in the head, which went off easily "in large sweats after a day's confinement."[1]

In 1712 there is mention of a "new ague," and about this time the term "la grippe" came into use. In 1727-29 there was a constitution of agues and other fevers, in the midst of which occurred horse-colds and epidemic catarrhs affecting human beings. A writer on one of the latter in 1729 refers to the "profuse sweats."

The great influenzas of the eighteenth century were those of 1733, 1737, and 1743. The first was a widespread fever, with catarrhal symptoms, and "the sick were in a general way much given to sweats" (Huxham); it was preceded by a disease of horses. The outbreak of 1737 was also preceded by a horse epizootic; sweats occurred as before, and "after the fever was totally gone there often remained obstinate rheumatic pains" (Huxham). The epidemic of 1743 is that referred to by a writer in the *Gentleman's Magazine* as "the disease called influenza in Italy." Horace Walpole dubs it "the blue plagues," and says whole families were attacked. Huxham says: "The greater part by far of the sick had easy, equal, and kindly sweats the second and third day."

Between 1743 and 1762 there was no universal cold, but localised influenzas occurred, associated in Scotland (1758), in Dublin (1750-52), and in England (1760) with horse-colds. In the great influenza of 1762 perspiration was "a constant symptom" (Baker). Heberden describes an epidemical cold in 1767. Fothergill notes that horses and dogs

[1] Short describes the Dunkirk rant of March, 1710, "a catarrhous fever, which lasted eight, ten, or twelve days," and was accompanied by "great pain of the head and all over the body;" he says it was brought over by disbanded soldiers.

were attacked in 1775, and mentions that servants, "especially the men who were most abroad," suffered from influenza in that year.

References to "a crisis by sweat after a few days" (Fothergill); "sweats which came on spontaneously" (Haygarth); "considerable sweats" (White); "a plentiful easy sweat" (Glass); and "warm copious sweats" (Reynolds) occur in connection with this epidemic. Glass's account is particularly interesting: he refers to attacks in institutions; he speaks of "a spontaneous sweat being the natural remedy of the fever;" he even uses the identical expression, "a Diary fever" applied by Caius to the sweating sickness of 1551; finally, he refers to horses and dogs being attacked, as do Haygarth and Pulteney also. In 1782 there came a "wave of catarrhal fevers" in the midst of a "great constitution of epidemic agues." Gray[1] says the disease came from Moscow and St. Petersburg, possibly from China, and adds that a similar disorder prevailed in the East Indies. He and others refer to perspirations, and Carmichael Smyth remarks, it "might very properly have been named the sweating sickness, as sweating was the natural and spontaneous solution of it."

During the years 1780-85, dog and horse outbreaks occurred, and in a "partial influenza" of 1788, dogs, horses, and cattle suffered. A remark made by Warren, of Boston, concerning the latter part of the epidemic of 1789-90 in that city is worthy of attention. "The sweats with which this disease terminated," he says, "were by no means so profuse as in the (preceding) autumnal epidemic." He even suspects he may be dealing with a new disease.[2] He is troubled at its sudden return in his city, observing that "the periods of 1510, 1557, 1580, 1587 and 1591, 1709, 1732 and 1733, 1743, 1762, 1767, 1775 and 1782, are much more distant" (*i.e.*, than from fall to spring, as in Boston).

[1] Gray's references to Macqueen's observations are noteworthy; for example, the sudden involvement of a ship's company in the case of the *Fly* sloop of war; his beliefs that the disease is "communicated by human effluvia and not by any matter generated in the atmosphere alone;" and that it occurs "ten or twelve times in the course of a century at no regular or certain periods;" his mention of "bold sweats;" and his confirmation of the account which had already obtained currency of the "strangers' cold" of St. Kilda.

[2] In the observations by the College of Physicians on this epidemic there occurs the passage "Nor was spontaneous and profuse sweating so general a symptom of the last influenza as it was of that of the year 1762."

Coming now to the nineteenth century, in the influenza of 1803, mention is made of "a gentle sweat in recovering after about a week less or more."[1] Burne alludes to perspirations in 1831, and there are in that epidemic, as also in 1803, numerous references to disease in horses and other animals. The influenza of 1833 was mild, the symptoms "going off with a sweat in the night;" "perspirations and soreness pervaded the skin" (Hingeston), but, "the perspiration was not critical."[2] This epidemic was followed by minor catarrhal attacks, and then by the sudden, simultaneous, universal influenza of 1837—again followed by smaller outbreaks, culminating in that of 1847-48. The "tendency to perspiration," and in certain places to "local rheumatic neuralgia" as a sequela (Streeter). and to "profuse perspiration" (Bryson), was noted in 1837. The epidemic of 1847-48 fell largely on the richer classes, and deaths in considerable numbers occurred as late as 1855.

Influenza in the past has thus been emphatically a sweating sickness, and this feature is apparent enough in modern descriptions of the disease. Bruce Low, in Parsons' Report speaks of "profuse perspiration;" Leichtenstern says that hyperidrosis is "an important symptom," and talks of "profuse sweats" and "extensive miliary eruptions;" Goodhart remarks that "a common and characteristic symptom, at any rate after two or three days have passed, is the occurrence of drenching sweats;" Hood[3] refers to copious perspirations as valuable aids to diagnosis. It may be that as many recent prevalences of influenza have fallen in winter time, sweating has been thrown rather into the background. The five English sweats occurred in summer, and in the summer outbreak of 1891 sweating was unquestionably a prominent symptom (see Bruce Low on "Influenza in Derbyshire in 1891."—Parsons' Report).[4]

[1] The *Memoirs of the Medical Society of London* (vol. vi., pp. 359-361, p. 278, p. 399), and Pearson, Carrick, Falconer, and Nelson Scott, all speak of sweats or perspirations.

[2] In this outbreak horses were attacked (Youatt), and the rich mainly suffered, the symptoms being those of catarrh, "ending in a sweat after two or three days with the usual head pains," and the like. Later, the symptoms became those of a more "adynamic" illness.

[3] *Lancet*, Dec. 30th, 1905, p. 1881.

[4] Sweating was not invariable in the fifteenth century. To those who did not sweat, "a flour of mace with warm beer (was) given, and then they sweat." Hecker says: "One form of this disease appeared that was wanting in precisely that symptom that was most essential—namely, the colliquative sweating."

On other features common to sweating sickness and influenza, the relapses[1] for example, more might be said, but of chief importance is the close epidemiological resemblance of the two maladies. Writing of influenza, Creighton says: "What kind of infection can that be which has befallen men on both sides of the Alps within the same short time, in the twelfth century as in the nineteenth, which has lasted unchanged through so many mutations of things, from mediæval to modern, and from modern to ultra-modern?" The English sweat, too, he finds was "volatile in its manner of travelling, like dengue, influenza, and others of the posting fevers of former times," yet, as we have seen, he does not admit the identity of the fifteenth and nineteenth century sweats, but accepts a strange theory which has had a remarkable vogue, and reference to which will serve as an introduction to other members of the sweat family.

Popular rumour is said, by Creighton, to have associated the original outbreak of English sweat with the arrival of Henry VII.'s mercenaries in England. Forrestier notes that the disease "first unfurled its banners in the City of London on the 19th September." There is, however, an entry in the *Croyland Chronicle* which suggests that the sickness may have been present before the mercenaries arrived, for Lord Stanley is reported to have excused his non-appearance at Bosworth Field, on August 22nd, because he was suffering from the sweating sickness. There is nothing to show that the mercenaries were ever ill, and, as Creighton remarks, Hecker has passed "clean into the region of conjecture in assuming that the sweat had arisen among them on the voyage and on the march to Bosworth."

It was pointed out, however, in the *Quarterly Review* of January, 1887, that the nationality of the mercenaries might be regarded as affording confirmatory evidence. They are stated in Hall's *Chronicle* to have been "a scum of Bretagnes," but Creighton gives reasons for concluding that they were Normans; and then adds that in the early part of the eighteenth century "an almost identical type of disease began to show itself among the villages and towns of that very region of France, the lower basin of the Seine, where the mercenaries of 1485 had been recruited."

[1] In the sweating sickness sufferers are said to have presented "repetition of the disease, even to the twelfth time."

Hecker had already pointedly called attention to the similarity between the Picardy and English sweats, but the former he considered could not "have proceeded from the English sweating sickness . . . a whole century . . . and what vast national revolutions" having intervened. He, moreover, laid stress on the "similarity and isolation of all the five epidemic sweating fevers . . . and the absence of all transitional forms of any duration, which certainly would have existed had Nature intended gradually to form a miliary fever out of the English sweating sickness." Creighton, however, cites instances of spread of disease among strangers by healthy persons, and holds that the English sweat "had a real relation to the seats of the Norman and Picardy sweat."[1] He goes further and argues that sweats are soil diseases, and in this finds explanation of the "clear intervals of many years" and "sudden bursting forth anew;" he adds, "What became of the specific virus from 1485 to 1508, to 1517, to 1528, to 1551 and after?"

Two facts appear to deserve mention here: first, communication with the Continent was to a far larger extent limited to the summer months in the fifteenth and sixteenth centuries than is now the case, and each of the five recorded outbreaks of sweating sickness, as a matter of fact, occurred in summer: second, the great trade relations of Tudor times were with the Hanse towns.[2] It will be

[1] Having in view the fact that the Picardy sweat was by no means confined to Picardy, it seems useless to labour the question of the origin of the mercenaries. There is no evidence that the Picardy sweat existed in the fifteenth century, the records commence in 1718. Oddly enough, according to the chroniclers, when the English sweat overran the Continent it avoided France.

[2] As Creighton says: "While the Portuguese and Spaniards were navigating in tropical waters, the English and French were sending most of their expeditions to the North;" or to quote another authority: "English commerce was chiefly carried on by means of the English Channel and the German Ocean, and the maritime enterprise which English seamen naturally emulated was not that of the Italian Republics but of the Hanse towns. In *Hakluyt's Voyages* there is an account of "The Discovery of Muscovy" in 1553, enterprised by Sir Hugh Willoughby and performed by Richard Chanceler. Many years before, this trade with the Hanse towns had reached its climax. "Lord Novgorod the Great," as the most easterly Hanseatic municipality styled itself, was in the fourteenth century a city with 400,000 inhabitants, the territory under the control or influence of which stretched from the White Sea to Lithuania, and from the Gulf of Finland to the principality of Vladimir. This city joined the Hanseatic League in 1260, and it no doubt had direct communication with London in 1485 and in subsequent years.

remembered that when the fourth sweating sickness of 1528-29 invaded the Continent these very towns were specially attacked; and, having in view the subsequent behaviour of influenza—in 1729, 1732, 1742, 1781, 1788, 1799, 1833, and 1889, it advanced upon Europe from the furthermost parts of Russia—it may be surmised that it was from the Baltic that the English sweating sickness came.

Great interest none the less attaches to the sweating sicknesses of Europe, among which this Picardy sweat has received special attention. Hirsch has fully discussed the confusion engendered in the seventeenth and eighteenth centuries by selection of a variable exanthem, presenting itself as a symptom in numerous maladies, for designation as a disease entity. Hoppe and Welsch described a miliary eruption in a disease of puerperal women—doubtless the present-day puerperal scarlet fever—and inasmuch as this "childbed purples" was associated with sudamina it became the fashion to describe all maladies in which sudamina occurred as "purples." Puerperal fever and rheumatic fever, says Immermann, were doubtless often thus designated, and to these may probably be added influenza, cerebrospinal fever, relapsing fever, and other diseases. Both Hirsch and Immermann emphasise the unreliability of the early records; but Hirsch, following Hecker, collected particulars concerning 194 outbreaks of "suette miliare" occurring between 1718 and 1874 in Picardy and elsewhere; and the existence of a disease species standing out from behind all the "friesels" and "purples" of the older writers has become quite an accepted doctrine.

Now, the accounts given of the Picardy sweat are to a large extent open to the criticisms which Hirsch and Immermann direct against seventeenth- and eighteenth-century "friesels" and "sweats" generally. Hecker selects "one of the most ancient" (Abbeville, 1733), and also "one of the most recent" (Oise and Seine et Oise, 1821), and concludes, from the particulars given, that "the miliary fevers, which have appeared in France in recent times, do not differ in any essential point from those of more ancient date." The two descriptions relied upon are, however, far from being convincing in regard to this matter; and it would appear probable that some of the outbreaks included in Hirsch's catalogue were really typhus fever, possibly associated with relapsing fever, notably that in Languedoc in 1782 (with its strange exanthem described

by Pujol) which in a few months carried off 30,000 people: some again were presumably relapsing fever (for example. the London outbreak of 1741); a number were almost unquestionably influenza (Arbuthnot says the influenza epidemic of 1733 ended "in miliary eruptions" in France); others finally may have been cerebro-spinal fever.

A study of Hirsch's table shows that 90 per cent. of the outbreaks from 1718 to 1832 were practically confined to Picardy and its near neighbourhood, whereas from 1833 onwards they range far more widely over France. Hirsch writes as if there was little doubt as to the identity of the outbreaks which he describes; but Rayer, from whom he takes his information (his tables are lifted *en bloc* from Rayer's book), speaks with much diffidence on this subject.[1]

Reference to English records shows that relapsing fever first began to make its mark about the time when the Picardy sweat appeared. Creighton refers to a supposed case in London in 1710, to the outbreak of 1727-29, in which sudamina are described, to cases in Edinburgh in 1735 accompanied by large plentiful sweats, and to Rutty's cases in Ireland in 1746, with miliary pustules and relapses. Indeed, in England between 1750 and 1760 there arose a controversy "as to whether there was in reality a distinctive kind of fever marked by miliary eruption," some contending that the phenomena were caused by the mode of treatment, others arguing as did Rayer and the historians of the Picardy sweat, that "miliary fever was a natural form.' Fordyce, in 1758, wrote his "History of a Miliary Fever, and Ormerod described the relapsing fever of 1847 under the same title. With all this it may be borne in mind that the scene of Marlborough's wars was largely laid in Flanders; Ramillies, Oudenarde, and Malplaquet lie just

[1] Indeed, he says: "L'expression 'fièvre miliare' a été employée pour designer des maladies si différentes qu'il y a réellement des épidemies qui n'ont de commun que les titres des ouvrages où elles sont décrites." Furthermore, it transpires from Rayer's account, that with regard to many of the outbreaks he had no information beyond the fact that "suette miliare" was reported to have occurred at the place in question. Again, his report shows that in many instances where only a particular village or commune is mentioned, the disease was really fairly widespread. Thus, under *Epidémie de Suette à Fréneuse* (1735), we read: "A la même époque la suette regnait également dans les environs de Paris, à Meaux, Villeneuve, St. Georges, dans le Vexin français et normand" (p. 430). Again, "Paris was attacked in 1747 (p. 448); Orleans, and the environs of Paris also, in 1733" (p. 447).

north of Picardy, and upon Picardy the French armies must have been largely dependent for supplies. Guizot writes that in 1708 "the destitution in France was fearful;" and again, when peace was concluded at Utrecht, he says, "The peasantry were reduced to browse upon the grass in the roads, and to tear the bark off the trees and eat it." Carlyle tells how (in the years when the "sweat" prevailed in Picardy) Paris was cleared out periodically by the police, "and the horde of hunger-stricken vagabonds . . . sent wandering over space . . . for a time." Here was scope for famine fever, truly, and there can be little doubt that many of the early Picardy sweats were of that nature. The descriptions given by Rayer do not, it is true, correspond with those of nineteenth-century authors, in that the critical sweat seems, as a rule, to have appeared earlier than the fifth day, and the relapse (when noted) earlier than the fourteenth. Koch, however, in recently describing relapsing fever in East Africa, comments upon the short duration of each attack.[1]

When influenza left Europe in the "'fifties," Picardy sweat practically disappeared also. There were sporadic prevalences in the "'sixties," including a more extensive one in 1866, and a few in the early "'seventies." In 1887, however, a very aberrant, or, as the French authorities say, bizarre form of Picardy sweat, appeared in Poitou, of which more anon.[2]

[1] There can be no question as to many of the later Continental sweats being influenza, but Rayer, it is interesting to note, comments on the fact that Mead described the sweat as being imported into England in 1713; this was, of course, the famous "Dunkirk fever" or "Dunkirk rant" of that year. Another reference of Rayer is very instructive; his outbreaks occurred as a rule between 43 deg. and 59 deg. north latitude (though Hecker includes an outbreak in London), but he points out that M. Degenettes has described miliary sweat at Gizeh on the Nile. This outbreak which, had it occurred nowadays, would no doubt have been called dengue, serves to link up in a most unexpected manner identical diseases occurring under very differing conditions, in distant countries, and removed from one another by long intervals of time. Geographically, it is interesting to note that of 89 departments in France, no fewer than 55 are included in Hirsch's list of 194 outbreaks, though a strip of territory in the north-east of the country has been especially involved; and in this it has been two departments close to Paris (Seine et Oise and Oise) and the department Bas Rhin, which have especially suffered. It is not a little curious to find that "suette miliare" repeatedly affected country districts not far removed from the capital, at a time when influenza is admitted to have prevailed in Paris itself.

[2] Immermann quotes a few recent instances of "Schweissfriesel" which he regards apparently as examples of the true idiopathic sweating

Hecker includes among sweating sicknesses the "cardiac disease" of the ancients and the Roettingen sweating sickness. The former, it seems, was compared by Houlier to the English sweat, and later writers feel therefore under obligation to refer to it. The full description given by Hecker suggests that it was a kind of olla-podrida of disease, and of its epidemiological features nothing is known. On coming to the Roettingen sweating sickness of November, 1802, we may clearly claim to be on familiar ground. In this little community of about 250 country people, living in a village surrounded by mountains, some 20 miles south of Würzburg, "strong, vigorous young men" were suddenly seized with "unspeakable dread" and developed "profuse, sour, ill-smelling perspiration," with "lacerating pain in the nape of the neck," while "in most cases all this occurred within 24 hours."[1] Now, when Roettingen was thus attacked, influenza, according to Hirsch, was prevailing in Germany; accounts are forthcoming from five localities only (Frankfort-on-Main, Cologne, Mayence, and Hanau, in February; and later, in April, Paderborn), and, curiously enough, three of the five are in the neighbourhood of Roettingen. To demand, therefore, as Hecker does, that the "mist-born spectre" of 1529 should be newly "drawn from the clouds into the midst of Germany" is entirely superfluous.[2] He writes, however, "We do not hesitate . . . to pronounce the Roettingen fever to have been the same disease as the English sweating sickness;" and here we may agree

fever, but his account of this supposed disease really adds but little to Hirsch's. The Hallerndorf outbreak of July, 1888 (Riedel, *Münchener Medicinische Wochenschrift*, 1889-90), only consisted of 14 cases (two men and 12 women) with four deaths. The Gurkfeld outbreak (Drasche und Weichselbaum, *Wiener Medicinische Blätter*, 3, 1892), appears to have prevailed coincidently with cerebro-spinal fever, and it was a very fatal one, there being 14 deaths among the 57 cases.

[1] It is noted "that the patients though bathed in perspiration had very little thirst, and the tongue was not dry, nor even foul, and maintained its natural moisture:" a statement which may be compared with "the tongue was as moist as in perfect health" (Picardy sweat at Abbeville, 1733); or "In influenza [the tongue] is usually moist or only slightly coated" (Leichtenstern, when speaking of influenza in the "'nineties").

[2] The only account of the disease extant emanates from an observer who "arrived only a few days before the sickness came to an end:" scarcely an authority to call up an extinct disease from a vasty deep of 250 years.

with him, adding the conviction that both were influenza."[1]

There now remains to be considered yet another sweating sickness, a malady, too, of the "posting" character—viz., dengue.[2] Just as the first sweating sickness was supposed to be peculiarly English, so this last sweating sickness has been deemed to be exclusively tropical; there is, perhaps, as much to be said for the one view as for the other. In Paris, on the outbreak of Influenza in 1889, an animated discussion arose as to whether influenza or dengue was in question.[3] De Brun, of Beyrouth, had described the latter as it occurred in the Levant, and the manner in which it was continuous in south-eastern Europe "with the succeeding influenza." His memoirs came under discussion when Paris was attacked by influenza, and the question as to the relationship of the maladies was naturally raised. Rouvier, in his *Identité de la Dengue et de la Grippe Influenza*, has strongly maintained that the two diseases are one and the same. Ringwood says that he observed dengue (introduced from Egypt by troops in 1885) at Kells, in Ireland, and watched it gradually becoming merged into the influenza of 1890; he considers that his neighbourhood for five years suffered from "influenza complicated by dengue, or dengue with modified cases which are commonly called influenza;" and he adds, when dengue "is widespread over tropical countries . . . the British Isles are visited by so-called influenza, which I maintain is dengue."

[1] Apropos of sweating sickness, Hirsch has some interesting remarks on "the coincidence in time and place of the epidemics of miliary fever and cholera." He finds that in 1832 cholera and miliary fever spread simultaneously in the departments of Oise, Seine et Oise, and Pas de Calais. Again, "The same fact was observed over a larger area in the second epidemic of cholera in France in 1849." Moreover, in 1853 the two diseases occurred side by side, and elsewhere similar coincidences were observed: in 1852 in Meiningen, and in 1849 and 1866 "at many places in Belgium and Luxemburg." Curiously enough, in this country a similar coincidence in time and place has been observed between influenza and cholera (Thompson, Bristowe); and Hecker from Germany notes that "the influenza of 1831 was immediately followed by the Indian cholera." Is there not here further reason for concluding that influenza and some of the miliary fevers are closely akin, if not identical?

[2] I had the opportunity, some years ago, of studying the papers relating to this disease collected by the late Dr. Christie, which were entrusted to me by the late Dr. J. B. Russell and by Sir Shirley Murphy, and are now the property of the Epidemiological Society.

[3] The same topic was debated in the *Lancet* and in medical circles in India (Sandwith: *Lancet*, July 5th, 1890).

Again, Dabney gives an account of an epidemic resembling dengue which prevailed in and around Charlottesville and the University of Virginia in 1888, and there is a notable account by Godding of an "obscure outbreak of dengue" on the *Agamemnon*, in the Indian Ocean in 1889, with the remarkable postscript: "Since writing the above, H.M.S. *Agamemnon* has returned to Malta, where influenza has been rife. The crew of this ship have suffered much less up to the present than any of the other ships. Has the dengue protected us?"

Very interesting, too, are the Queensland outbreaks of dengue of 1897-98 and 1905 (*Intercolonial Medical Journal*, Australasia, 1897, 1898; *Australian Medical Gazette*, 1897; *Journal of Tropical Medicine*, December 15th, 1905). The resemblance of the pains to those of influenza, the absence of some of the symptoms usually regarded as characteristic of dengue, and the conviction expressed by some observers that the disease was "that we call influenza in England," are specially noteworthy. Once more there may be cited the recent dengue outbreaks in the East Indies, described by Stedman (*British Medical Journal*, July 12th, 1902); some of the cases would have been thought to be influenza "had it not been for the prevalent epidemic of dengue." Note may also be made of the dengue with coryza, and "at times catarrh of the throat and trachea," at Hong-Kong in 1895. Finally, the testimony of Domenichetti, referred to by Parsons (*First Report*, p. 55), may be adduced. Against all this must be set the evidence quoted by Leichtenstern and Parsons. The former cites Zülzer, von Düring, and Skottowe, the latter Sandwith and Limarkis—all observers who had seen both diseases. Leichtenstern's witnesses deal with the epidemiological side of the question, and will be referred to later. Sandwith and Limarkis lay stress on clinical distinctions. It may be noted, *inter alia*, that the former considers the dengue of Egypt to be less severe than that of India, Aden, and the United States, and says "there are many varieties of dengue," and he adds it resembles influenza in that "epidemics differ from previous outbreaks;" while he and Limarkis agree that convalescence from the disease they regard as being "influenza" is usually rapid.

The clinical differences upon which emphasis has especially been made are the initial and terminal rashes, and the joint affections of dengue, and the catarrh and lung and nervous complications of influenza. But exceptions

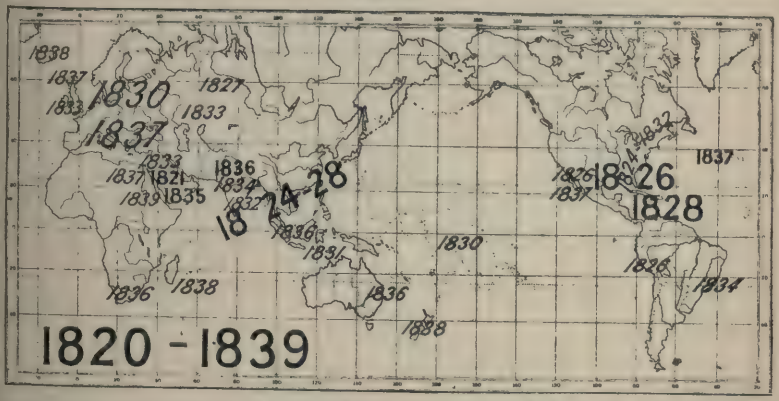
are the rule. Again and again lung complications are absent in influenza. This was originally noticed by Henisch "in the first outbreak of grippe in 1580," and subsequently by numerous observers, and even as late as 1890. On the other hand, they may occur in dengue (von Düring; Hong-Kong epidemic, 1895). The rash or rashes of Dengue are by no means invariably met with (Skottowe's account and the Queensland epidemics). The terminal rash may be miliary in form (Holliday, New Orleans; and Thomas, Charleston): and rashes—morbilliform, scarlatinal, urticarial, and miliary —may occur in influenza. In the later epidemics of dengue, swelling of joints has been uncommon (de Brun, Mordtmann, von Düring, and Skottowe), and joint pains may occur in influenza (Bristowe). As instances of the confusion which reliance upon clinical distinctions may produce, the Queensland epidemics and that described by Skottowe (Epidemiological Society's *Transactions*, 1889-90) may be referred to, or the outbreak in Fiji in 1890 may be cited. We are told there was no influenza in Fiji in that year, but "a prevalence of catarrhal complaints was met with . . . and about the same time a few cases of smart fever, with headache, pains in the eyeballs, quasi-rheumatic pains in the limbs, and blotchy-red rash were observed, but these were recognised as dengue." (Parsons, *First Report*, p. 49.)

If we turn from clinical to epidemiological distinctions, confusion becomes worse confounded. Most remarkable of all is the manner in which, on an extended historico-geographical survey, the two diseases are interchangeable with one another. Thus the repeated invasions of the West Indian islands by influenza in the latter part of the eighteenth and early part of the nineteenth centuries are well attested (Figs. 1 and 2); but between 1820 and 1840, when influenza was almost pandemic, there was in the West Indies no influenza, but a severe outbreak of dengue (Fig. 3). Contrariwise, between the epidemics of 1850 and 1905, despite its existence elsewhere, no dengue, only influenza, is forthcoming from these islands (Figs. 4, 5, and 6). In 1826-28, "dengue" raged in the West Indies, in the Southern States of the Union, and in the north of South America (Fig. 3). Coincidently, "influenza" was prevalent over the Western Hemisphere, and notably in the Southern States of the Union, in Mexico, and in Peru. In 1849-50 dengue became diffused over these Southern States (Fig. 4), and simultaneously influenza prevailed in the Northern States.

Fig. 1.

Fig. 2.

Fig. 3.

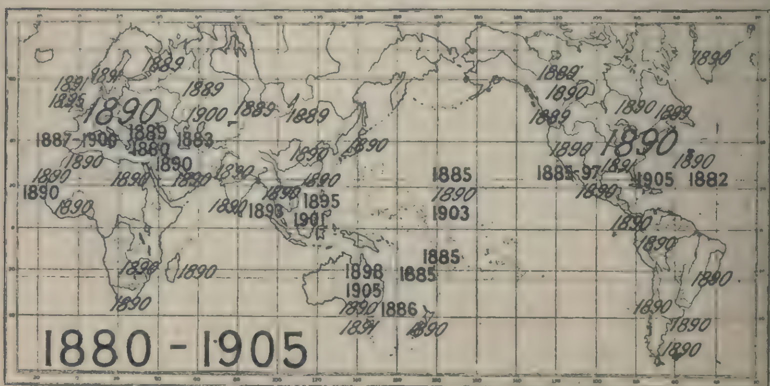


Geographical Distribution of Outbreaks of Dengue and Influenza during successive Periods of 20 Years. The dates given in ordinary figures are those of major or minor prevalence of dengue, while italic figures relate to influenza outbreaks.

Fig. 4.

Fig. 5.

Fig. 6.



Geographical Distribution of Outbreaks of Dengue and Influenza during successive Periods of 20, and finally of 26, Years. The dates given in ordinary figures are those of major or minor prevalence of dengue, while italic figures relate to influenza outbreaks.

Dengue was in Alabama and Louisiana in 1873, and in that very year influenza was reported from the West Indies, and was spread abroad over the United States (Fig. 5).

With these phenomena in the Western Hemisphere may be compared the behaviour of the two diseases in India and the East Indies. Taking the widespread influenza epidemic of 1781-83, India suffered, and coincidently India and the East Indies presented a dengue prevalence (Fig. 1). In 1824-28, influenza was confined to the Western Hemisphere (save for outbreaks in Russia and Siberia); dengue prevailed in India and Further India. In 1831-37, India and Further India, with the rest of the world, underwent attack by influenza (Fig. 3). In the next period of widespread influenza, dengue alone is reported from India and Further India (Fig. 4). Again in the "'seventies," when influenza is diffused over North America and Europe, dengue alone appears in India and the East Indies, but it is then as widely distributed as is influenza in the regions it affects (Fig. 5). The escape during recent years of places in the Western Hemisphere, formerly favoured seats of dengue, and their involvement in influenza prevalence, may be set against the fact that in the East Indies, China, and Australia, dengue has been reported from localities which suffered but lightly in the last great influenza pandemic.

Two outbreaks which illustrate points already discussed may be here referred to. Dr. R. A. Dunn, in the winter of 1904-05, encountered in East Herts "an epidemic simulating influenza."[1] The disease was widespread, of low morality, and mainly affected children. Relapses were common, convalescence was prolonged, a few cases presented a rash, and later desquamation, and in at least one instance a miliary eruption was observed. The disease assumed three types: scarlatinal, cerebro-spinal, and typhoidal; but Dr. Dunn concluded that he was dealing with one disease, for the different types were commonly associated in the same household.[2] The student of influenza outbreaks is so accustomed to finding influenza described as a new disease,

[1] A conference of Hertfordshire Medical Officers of Health was convened by Dr. F. E. Fremantle, at which I was permitted to be present. Dr. Lovell Drage and I urged at this conference that the outbreak was one of influenza.

[2] Dr. M. H. Gordon, who made a bacteriological examination of material obtained from the later cases, only exceptionally found Pfeiffer's bacillus, but almost always the micrococcus catarrhalis.

that the fact that the East Herts epidemic was credited with being the first of its kind is not altogether surprising; yet in Parsons's report the difficulty of distinguishing influenza from scarlet fever and cerebro-spinal fever (the diseases from which diagnosis was held to be most difficult in East Herts) is noted and, as a matter of fact, influenza, so called, was prevalent in London and in other parts of England when the East Herts prevalence occurred. A point of special interest in the outbreak is undoubtedly the occurrence of secondary or terminal rashes (described by Clark, Thresh, and others), for it would appear that when "influenza" *escapes*, as it were, from the now well-nigh immunised urban populations of this country, and *sports* in a comparatively sparsely-populated rural district, it assumes close resemblance to dengue—indeed, had the East Herts outbreak occurred in a tropical town, I am assured by an observer who has seen dengue in the Tropics, that it would undoubtedly have been regarded as an epidemic of that disease.[1]

The second outbreak, half sweat, half measles ("moitié rougéole et moitié suette") occurred in Vienne in 1887, and was reported upon by a Commission with Dr. Brouardel at its head.[2] It was declared to be Picardy sweat (of which very little had been heard for half a century), or at least a "suette à forme rubéolique," and the Commission refers to outbreaks presenting this "bizarre" form in Périgord in 1841, Poitiers in 1845, Seine et Oise in 1861, and Pas de Calais in 1864. The affinity of the Poitou disease to dengue and to the East Herts outbreak—*i.e.*, to influenza—must strike the reader of the French Commission's Report.[3]

[1] The Hertfordshire epidemic presents some resemblance to the outbreaks of illness with cerebro-spinal symptoms described by Bruce Low; *e.g.*, that at Raunds in 1891, Laxfield in 1894, and the anomalous influenza of Market Rasen and of a Shropshire village in the same year (see *Reports of the Medical Officer of the Local Government Board* for 1890, 1891, and 1894, and the *Transactions* of the Epidemiological Society for 1898-99); outbreaks which Bruce Low found difficulty in deciding to his complete satisfaction were not really outbreaks of influenza.

[2] *Bulletin de l'Académie de Médecine*, 1888.

[3] The villages and towns in an area some 70 miles by 50 in extent, to the south-east of Poitiers were involved. In some instances, whole families were prostrated, the elders with "sweat," the children with a disease accompanied by a morbilliform eruption. Relapses were common, the disease was specially apt to be severe in male adults; the case-mortality ranged from 3 per cent. upwards. As regards diagnosis,

It may be urged, however, that admitting the close clinical resemblance between dengue and influenza, and the curious coincidences presented in their historico-geographical record, there are certain epidemiological distinctions. Thus some observers have maintained that dengue spreads comparatively slowly from person to person, while influenza extends far more rapidly, and presumably by atmospheric contagion.[1] The thesis that influenza travels more rapidly than can be accounted for by human intercourse has, however, been disposed of by the more complete records of recent years, and is universally discredited. Leichtenstern's references to the fact that Zülzer and von Düring held dengue to be contagious, influenza not contagious, while he himself maintained dengue to be "contagious miasmatic," and so on, have thus ceased to be of interest.

Turning now to the allegations that dengue is a coast disease and unable to rise to any altitude, Manson points out that there are many exceptions. Thus, "in 1870-73 it spread all over India;" again, he says, there is "a

influenza, la grippe, was not even considered by the Commission. Cough and bronchitis, sore throat, and coryza were present in some instances. Measles could be excluded, because communes which had recently suffered from measles were severely attacked by the "new disease." Moreover, the incubation period of the malady was short: only about twenty-four hours.

[1] Leichtenstern cites Skottowe's report on the dengue epidemic of 1885-86 in the Fiji Islands, as showing how a single observer dealing with the two diseases is able to discriminate between them. But the distinction upon which Skottowe mainly relies is the difference in the mode of spread—dengue "hugging the coast," influenza being "disseminated like the wind over all the islands"—and on this point Leichtenstern remarks: "The comparison is interesting, but the explanation is incorrect." As regards the existence of two or rather three epidemics in 1885-86 in Fiji, Leichtenstern says: "Just before and just after the dengue epidemic there was an influenza epidemic;" Skottowe's own account is to the effect that "a few weeks before, and continuing some little time after the dengue outbreak" influenza prevailed, or, as he elsewhere puts it, dengue "broke out during the prevalence of an epidemic of influenza." When it is added that the dengue "in many of its symptoms . . . differed considerably from that described . . . in the text-books;" that "the majority of cases . . . were not typical in the ordinary acceptation of the term;" that even in one house "one member of the family was suffering from influenza and another from dengue;" that the cases did not, as a rule, present both initial and terminal eruptions; that Skottowe saw no joint complications, and that muscular pains including "aching in the fibrinous tissues and tendinous insertions of the eyeballs," and marked and persistent debility in convalescence, were the prominent features in the so-called "dengue," it may be surmised that not three epidemics but one only was in question.

distribution and concentration of population on the seaboard and along rivers," and "the freedom of communication between communities so located probably determines this preference for such localities."[1] "In Queensland," in 1898, it was noted that the disease did "not hug the coast," but no doubt it often does; indeed, it might, *à priori*, be expected that when influenza spreads in the Tropics it would do so after the manner of "dengue," and not after that of "influenza," as observed in Europe and North America. Leichtenstern says, as a matter of fact, this is the case.

The most marked contrast of all is the limitation of dengue to hot countries. But here it should be noted that, coincidently with involvement of the West Indies and Southern States of the Union by dengue, influenza has prevailed in the Northern States. When Philadelphia suffered from the disease which Hirsch says was dengue in 1780 (a disease which, on reference to Rush's original account proves, however, indistinguishable from influenza), influenza prevailed in adjacent regions a little further north. In 1784, and again in 1788, "dengue" broke out in Cadiz, and accounts of influenza are forthcoming in those years from beyond the Pyrenees. Again, in 1863 and 1867, when dengue prevailed in Cadiz, influenza is reported from over the frontier. Leichtenstern says the dengue of 1784 in Cadiz and Seville was "probably carried by troopships which came from the West Indies," but neither he nor Hirsch[2] mentions the existence of dengue in the West Indies in 1784 or 1788. Similarly, Leichtenstern refers

[1] The observations as to escape of certain higher lying portions of the Island of Réunion are referred to by Hirsch and by Leichtenstern, and the latter says that similar observations have been made in "Cuba, Jamaica, Martinique, and almost everywhere," though he quotes an apparent exception in a hot year in Lebanon. "Les villages situés aux altitudes les plus élevées . . . le Liban, la plaine de la Becka, l'anti Liban . . . ne furent pas plus épargnés que les villes de la plaine" (de Brun). Leichtenstern notes, however, in 1890 the exemption from influenza of the Isle of Man, the Bahamas, the Seychelles, and other places, and that of the Säntis observatory population, 2,504 metres above the sea. Still more to the point is his statement that "influenza, too, although affecting both land and sea in the Tropics, was confined principally to the chief trade ports."

[2] Hirsch refers to the "perspiration with its pungent odour" in this outbreak of "dengue," and says the poor people called it "piadosa," or the merciful, because of its tendency to a favourable issue.

the Cadiz epidemics of 1863 and 1867 to the West Indies, "the home of dengue," though again the authorities are silent as to the existence of dengue in "its home" in those years. Hirsch makes mention, however, of influenza in France in both 1863 and 1867, and states that influenza was widely prevalent in Europe in 1781-82, and again in 1788.

Take, again, Arabia and North Egypt. Leichtenstern says that the principal epidemic years there were 1835-36, 1845, and 1868. Now, in 1835-36 influenza, according to Hirsch, was also prevalent in Egypt and Syria; while in 1846-47, and again in 1868, it prevailed in Turkey and Constantinople. What becomes, then, of the limitation of the spread of dengue by a particular degree of latitude? The merging of dengue and influenza in 1889, on passing from Egypt and Syria to Turkey and Greece, has already been commented upon. It is surely not a little remarkable that when North Europe (France, Germany, and Russia) present influenza and North Africa (Tripoli, Egypt) dengue, the intermediate countries, Spain and Turkey, yield evidence now of one and now the other disease. It may be added that several authorities deny that dengue is limited to the hot season of the year—*e.g.*, Thomas (Savannah, 1881), de Brun and Rouvier (Beyrouth, 1889), and writers on the Queensland epidemics of 1898 and 1905.

A further point must be considered, as it throws light on the likelihood of unreal distinctions between dengue and influenza being drawn. According to Leichtenstern, "influenza presents at least two phases, one pandemic and the other endemic, and they follow different epidemiologic rules."[1] He notes as characteristic of the so-called "trailing epidemics," diminished morbidity, less wide geographical distribution, scarcely recognisable communicability, slow development and extension, and continuous diminution in frequency and intensity. He speaks of a "successive lessening of the susceptibility of the population, due to their immunisation, etc.," and speculates as to whether "the germ continues to thrive in an attenuated

[1] He says: "At the beginning of the pandemic of 1889 the vis contagii was, as is well known, enormous; the vis morbi, on the other hand, was so slight that it gave rise to ludicrous names ('influenza dinners'). In the later epidemics the vis morbi became more pronounced with the decrease of the vis contagii, owing perhaps to the weakened influenza germs entering into closer symbiosis with other pathogenic microbes."

form in the nasopharynx of individual patients . . . the endanthropic attenuated germs" becoming virulent again after a time, and thus causing local epidemics.[1]

This is one way of regarding the phenomena. Alternatively, the behaviour of influenza in a densely aggregated population, its smouldering, and bursting into flame, may be explained as resulting from varying capacity of resistance to attack (see p. 54). Study of the recurrences of influenza in individuals may help to decide which view is the correct one. On the one hypothesis infection comes from within, on the other from without. If from within, the recurrence of disease in the individual might be expected to occur more or less independently of its prevalences in the community as a whole; if from without, the individual would, as a rule, suffer when the disease was widely prevalent. In the annexed diagram (Fig. 7) the attacks by influenza of seven members of a London household are exhibited in their relation with influenza prevalence in London between 1890 and 1905. The observations, as will be seen, fit in with the hypothesis of infection from without. The fact that influenza has "pandemic" and "trailing epidemic" phases is important, when it is recollected that, broadly speaking, the influenza countries include some of the most densely, and the dengue countries some of the most sparsely, populated parts of the world. (India and China must be left out of account in making this comparison, as so little is known of their diseases.) Thus, in influenza countries, "trailers" are commonly met with, while, in the dengue countries they are comparatively rare; in the former the disease is a "composite image" of the influenza of pandemic and trailing epidemic phases, and in the latter it appears more exclusively in pandemic phase. Does not this fact, together with differences dependent upon altered climatic conditions, explain the supposed distinctions between dengue and influenza.

[1] It is interesting to note that England, "the chief maritime country," as Leichtenstern terms it, was apparently infected from America (so he says) in 1891, Germany and France remaining almost exempt; on the other hand, when, after prevailing in North America in 1873, influenza invaded Europe in the following year England is said to have escaped. It may be that England which, as chief maritime country, had suffered so severely from 1833 to 1855, was comparatively immune in 1874; but the Registrar-General's returns seem to indicate that there was influenza in that year, and the fact must be within the knowledge of many medical men now living. I had what I believe was an attack of the disease in London in that year.

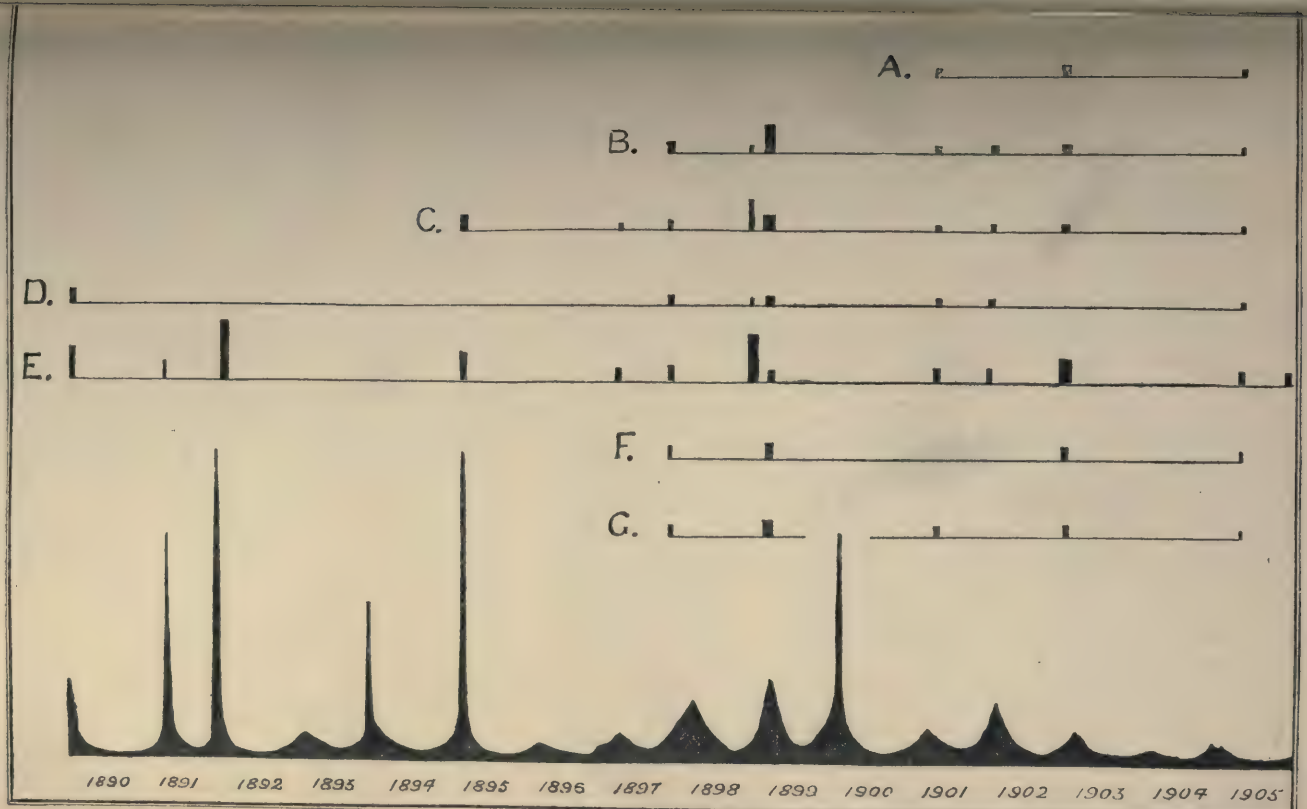


FIG. 7.—RECURRING ATTACKS OF INFLUENZA IN MEMBERS OF ONE HOUSEHOLD (LINES A TO G) IN RELATION TO INFLUENZA IN LONDON BETWEEN 1890 AND 1905.

The letters A to G indicate the points of time at which the several individuals come under observation. The rectangles indicating attacks are extended upwards in proportion to severity, and are broad in proportion to duration of illness.

If the two diseases be one and the same, it does not necessarily follow that the whole world must be swept in a pandemic. Leichtenstern notes that "in former times extensive epidemics of influenza occurred, limited to North America alone;" and in 1875 the Eastern hemisphere escaped lightly when North America was hard hit. There appears, therefore, to be an "alternating national immunity," as, indeed, Leichtenstern maintains is the case. Europe suffers heavily in the "'thirties" and "'forties" as compared with India, escapes lightly in the "'seventies," and suffers heavily again in the "'nineties," when India in its turn is comparatively immune. The records are far too imperfect to follow this out in detail; in particular, the absence of knowledge of the epidemics of the densely aggregated Eastern hemisphere populations prohibits this.[1]

On reviewing the history of influenza and dengue, it is clear that they afford abundant illustration of the manner in which fashionable theories colour accepted descriptions of disease. One feature, at any rate, is clearly brought out —the extraordinary similarity in their behaviour when they are in pandemic phase. The sudden onset, the tendency to relapse (with altering or modified symptoms), the establishment of greater or less degree of immunity in the populations affected, the "posting character" of the epidemics, the involvement of animals, the attack upon particular classes of the population and upon inmates of institutions, and the return after a number of years to the point of

[1] As there are sceptics who doubt the existence of influenza in this country at the present time, I may take shelter under the authority of Goodhart (Allbutt's *System of Medicine*), who believes "influenza is still with us." Those who differ may at least be asked to explain where they draw the line, *i.e.*, after 1890, or 1891, or 1892, or 1895, or when. It remains, however, to be said that the bacteriologist, to whom influenza connotes presence of the bacillus of Pfeiffer, has grave difficulties to contend with, if the trailing epidemics be regarded as influenza. In Kolle and Wassermann's text-book it is admitted that Pfeiffer's bacillus occurs in people who have not influenza, but this is justified by explaining that a similar phenomenon presents itself in diphtheria, cholera, and enteric fever. Ebstein (*Münchener Medicinische Wochenschrift*, 1904), finds Pfeiffer's bacillus often absent in influenza and present in other diseases; and numerous other observers might be referred to as having found it in measles, scarlet fever, whooping cough, &c.; Washbourn and Eyre (*British Medical Journal*, December 20th, 1902), demonstrated it in cases they describe as "unrecognised cases of influenza." *La Semaine Médicale* (March, 1905, p. 103) contains an interesting discussion on the bacteriology of an outbreak in Paris (see also the *Lancet*, March, 1905), supposed not to have been influenza because Pfeiffer's bacillus was not forthcoming.

departure, completing the circle of events. If the range of vision be contracted to some twenty or thirty years, we are impressed with the rapid transformations presented; on a broad view, however, the type remains extraordinarily constant, and we are forced to the conclusion that apparent instability results merely from interplay between the germ and its environment. Not only in influenza, so-called, but in the dengue of the Tropics and the sweating fever of the fifteenth century, we may claim to discern the operation of a single disease entity. We may add with Hirsch, that "few among the acute infective diseases have manifested in their prevalence, at all times and in all places, the stamp of uniformity so strongly *in the aggregate of symptoms* as influenza."

LECTURE III[1].

MR. PRESIDENT AND GENTLEMEN: We have seen that influenza was prevalent in Europe and America during the early years of last century, that it recurred in the "'thirties" and "'forties," and recurred again in the "'nineties." A close parallel to these waves of influenza is afforded by the outbreaks of "throat distemper" in Europe and America in the "'forties" and "'seventies" of the eighteenth century. Records which tally closely with our modern delineations of disease do not date far back; even Sydenham, in his account of scarlet fever, makes no mention of sore-throat nor does Sibbald. Morton describes it as a "confluent measles." Willan, Wintringham, and Hillary include cases which would doubtless now be called diphtheria. Like difficulties are met with in the descriptions of Huxham, Fothergill, and of the Americans, Douglas, Colden, and Bard. All through the eighteenth century this confusion continues, and the frequent mention of miliary eruptions, complicates matters not a little. In 1777-78 Levison's and Wintringham's descriptions accord more closely with latter-day conceptions of scarlet fever. As to diphtheria, dimly discernible as "garrotillo," "morbus strangulatorius," and malignant, putrid, gangrenous, etc., sore-throat, it was only in 1821 that Bretonneau even gave it its name, and it is not until 1855 that scarlet fever and diphtheria are distinguished in our own official returns. Clearly, evidence of persistency of type manifested throughout a long period of time must not be looked for in throat distemper.

In the case of continued fever, the difficulties are even greater. Murchison suspects that the old Greek physicians saw and described typhus, relapsing, and enteric fevers, but the early records in this country are very perplexing. The famine fevers, gaol fevers, and later some of the ship and camp fevers, were presumably typhus fever, and in the seventeenth century this malady fairly settled down in the towns. It has been suggested that relapsing fever contri-

[1] Delivered on March 8th.

buted some of the material worked upon by medical writers in 1709 and 1710, and Rutty's description dates from 1739. The final differentiation of enteric fever from typhus is, of course, a matter of comparatively recent history. Two questions of special interest from an epidemiological point of view stand out very clearly. There is the ability of typhus fever to smoulder—it smouldered among the prisoners who infected those assembled in assize courts[1] in the sixteenth century, and it smoulders in London, Liverpool, and Dublin at this day. In the second place, there is the close relationship between relapsing fever and typhus, on which Murchison commented, and Fagge, Thompson, and others have laid stress. The distribution of prevalences of these maladies in time and space is strikingly similar; their relation to famine and their merging into one another in the same epidemic may be also referred to. Rabagliati says: "In epidemics of relapsing fever . . . even before it was properly distinguished from typhus fever, we find records of a low mortality as the epidemic advanced,[2] and of a mortality which was highest towards the close of the epidemic. This was particularly noticed in the epidemics of 1817-18 and in 1819. The most probable inference seems, therefore, to be that there was a mixture of cases of relapsing and of typhus fever, and that their relative frequency at different periods of the epidemic determined the observed mortality."[3]

In applying the historical method of inquiry to scarlet fever and diphtheria, and still more to continued fever, the

[1] The prisoners themselves were known to be ill in some instances. Alternatively infection was attributed to "devilishly contrived and obviously papistical spirits" (Oxford Black Assizes, 1577). Howard states that new convicts "may sicken and die in a short time with very little apparent illness." Bacon observes (*Sylva Sylvarum*) *àpropos* of jail smells, "they are not those stinks which the nostrils straight abhor and expel that are most pernicious, but such airs as have some similitude with men's body, and so insinuate themselves and betray the spirits."

[2] Murchison (p. 380) refers to Rutty's statement that "seventy of the poorer sort . . . abandoned to the use of whey and God's good providence recovered" (1739).

[3] This writer observed in 1869-70 that several patients who had contracted relapsing fever later developed typhus fever, but he did not meet with cases in which typhus was followed by relapsing fever. Recent investigation seems to point to the bug as the common means of conveyance of relapsing fever. In the Congo a disease closely resembling—if not identical with—relapsing fever is transmitted by ticks.

data are obviously less complete than in plague and influenza. The problems, on the other hand, which arise from the bacteriological point of view take perhaps more definite shape. To a still greater extent are divergencies of like sort apparent in dealing with tuberculosis. Historically there is little to guide us. The steady decline in the death-rate from pulmonary tuberculosis in the last fifty years has been attributed to the operation of a great variety of factors, among which cheaper food and improved hygienic surroundings, inheritance of capacity for escaping attack, weeding out of the less resistant, drying of subsoil, cyclical alterations of virulence, segregation of cases, and so on, have especially been mentioned. It is not unlikely that the supposed reduction is to no inconsiderable extent the result of altered nomenclature. In any case, the statistics admittedly become very unreliable after proceeding backwards for forty or fifty years. From the bacteriological point of view, the tuberculosis question is, however, most interesting. I do not propose here to do more than briefly note Arloing's conclusions, to which Dr. H. T. Bulstrode has drawn my attention, to the effect that the various tubercle bacilli "are only varieties of one and the same species, and that no marked delimitation separates them;" and, again, that they "form a sort of chain in which enter from time to time links bigger than the others, representing, so to speak, the types accepted by some bacteriologists."

It is generally admitted that the persistency of type displayed by measles and small-pox is quite remarkable. For that reason they afford specially promising material for study of short-period waves; and in turning, therefore, to the examination of variability of type these two diseases may with advantage be considered in the first instance. The simplest case is that of the short-period waves of measles. The explosions in towns occur commonly at about biennial intervals, "when the accumulation of susceptible persons is sufficient, and the climatic and other internal conditions offer sufficiently small resistance. . . . The mean seasonal wave shows two maxima—two points of least resistance six months apart," and hence the interval between the explosions, "when not exactly two years is frequently one and a-half or two and a-half years" (Whitelegge). The problem, in the case of measles in a large community, is much simplified; thus we are dealing with an obligatory parasite, and hence questions of

saprophytic growth, of food outbreaks, etc., do not arise; furthermore, one attack confers almost complete protection;[1] again, infection spreads readily from person to person, population being densely aggregated, and new susceptible material added in sufficient quantity and with sufficient frequency to favour stable epidemic movement.

I have taken the London figures, and assumed a case-mortality of $2\frac{1}{2}$ per cent. By first plotting out weekly numbers for periods selected as presenting typical epidemic movement, and then superimposing one wave upon another, a curve is obtained with a maximum of 6,400 cases (160 deaths), declining after an interval of 39 weeks to a minimum of 400 cases (10 deaths) weekly. Such a curve, with waves of approximately 18 months period, and maxima occurring alternately in summer and winter, furnishes the type to which London measles conforms (Fig. 8, p. 53).

The London population is augmented weekly by addition of some 2,500 susceptibles, or, allowing for the comparative insusceptibility of very young infants, and taking into account their high mortality from causes other than measles, say by 2,200 susceptibles. Furthermore, the incubation period of measles being approximately a fortnight, the 39 weeks (ML) may be looked upon as comprising $19\frac{1}{2}$ such periods. Up to the time of reaching A the number of cases is increasing, it then diminishes; similarly, up to the time of reaching K, the cases diminish and then subsequently increase. In passing these points increase is converted into decrease, or *vice versâ*, the tangent to the curve at the instant being horizontal and stationary. It will be apparent, therefore, that at A each case may be regarded as infecting one other case; this will also hold good at K.

[1] History of second attack by measles needs to be accepted with reserve. German measles and scarlet fever, at any rate, are often sources of confusion. The age-incidence of measles in large communities, and the fact of exemption, in communities attacked after an interval of years, of those who suffered in a previous outbreak, make it clear that the protection is of a lasting character. Brownlee found out of 12,000 cases of measles at Belvidere (Glasgow), 1885-1902, 71 were over the age of thirty; "these 71 were almost without exception persons born in the country, who had not passed through measles in early youth." Donald Hood has maintained ("An Enquiry into the Etiology of Rötheln") that rötheln is but a modified form of measles after all. His paper contains much of interest in relation to variability of type. In particular, a passage quoted from Bouchard may be cited, "Ce n'est donc pas à une attenuation de virus qu'il convient d'attribuer la décroissance des maladies infectieuses, mais à l'augmentation de l'immunité des hommes."

If the virulence of the measles organism and other factors be assumed to be the same at A and K, it will follow, inasmuch as each case is then capable of infecting one other case, that the number of susceptible persons in the population at those points of time will be identical.

If the ordinate BT be = 2,200, then at B the number of susceptible persons is at its minimum, for during the period M to T (A to B), those attacked each week outnumber the susceptibles newly added. At the corresponding point C the number of susceptibles is at a maximum, for the susceptibles newly added between K and C exceed in each week the number attacked.

Further, area ADB = area BHK: for the former represents the excess of persons attacked over susceptibles newly added in the time MT; and this must be equal to the excess of those newly added over those attacked in the time TL.

The areas ADB, BHK may be approximately determined. Area ADB is rather greater than

$$\frac{\text{AD.DB}}{2}, \text{ i.e., } \frac{(6{,}400-2{,}200) \times 14}{2}$$

and is thus = 30,000 approximately. Thus, during the period B to C, the number of susceptibles in the population must be augmented by some 60,000.

We may further determine the actual number of susceptibles at A, B, K, and C. It will be found that near B the cases occurring weekly fall from about 2,500 to 2,000. Assume the number of susceptibles at A to be x, the number at B will be $x-30{,}000$. If the lessened ability to infect at B be solely due to diminution in number of susceptibles we may write

$$\frac{x-30{,}000}{x}=\frac{2{,}000}{2{,}500}, \text{ i.e., } x=150{,}000 \text{ approximately.}$$

On this showing, the measles wave in London shows fluctuation from, speaking approximately, 150,000 susceptibles (at A) to a minimum of 120,000 susceptibles (at B), reached 14 weeks after A. At this point, B, instead of each case infecting another case, five cases approximately produce only four; the number must then further decline to about 400 a week (at K), when the susceptibles again attain to 150,000; proceeding onwards to C, the apparent infective power of each case continues to increase (on reaching C four cases approximately produce five), and the number of

susceptibles is at its maximum (180,000); but on proceeding further, it falls until it is again 150,000 at the crest of the wave. At C the condition $\frac{x+30{,}000}{x}=\frac{2500}{2000}$, if applied,

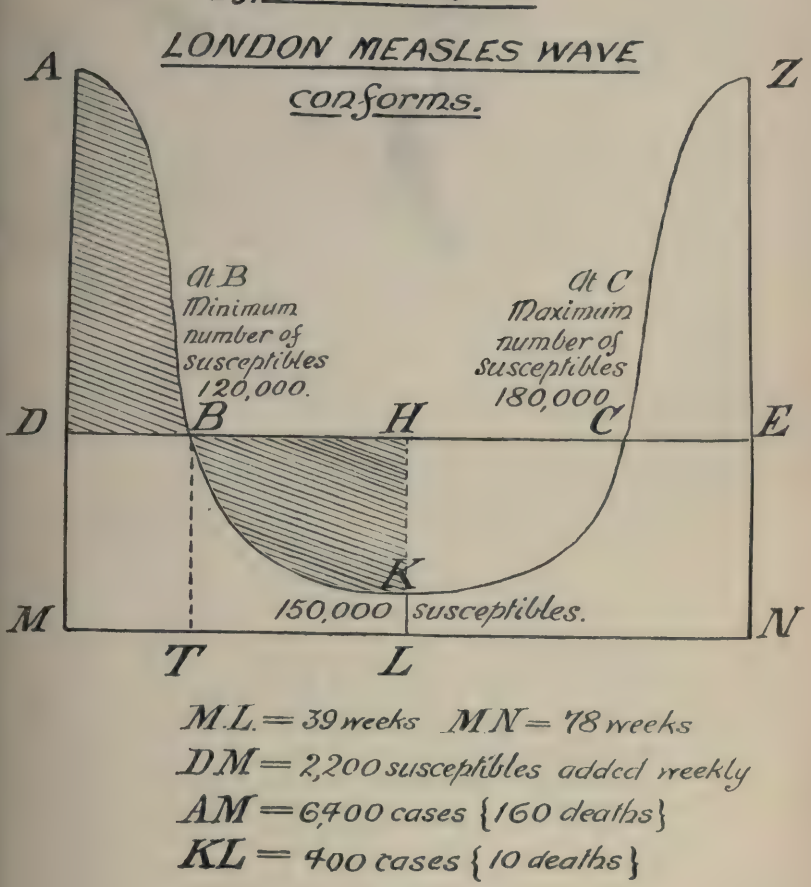


Fig. 8.

would give a somewhat lower value of x than that already obtained. In other words, the curve cannot be exactly symmetrical in relation to an axis drawn through HKL, and if we wish to be precise it should be "skewed"

accordingly. It is indeed remarkable, having in view the hypothetical character of some of the conditions laid down, and the extent to which disturbing factors (climate, school influence, differing densities of population, etc.), might be expected to operate, that the type is so consistently adhered to. This examination shows the absurdity of assuming that an epidemic comes to an end because all the susceptibles have been attacked; and, again, in measles at any rate, of explaining the decline by loss of virulence of the organism or of its infecting power. Dr. A. Davidson points out that "retardation in the rate of spread is not to be accounted for solely by the reduction in the actual number of the susceptible; for the number attacked subsequent to the slowing of the ratio of increase is greater than that up to the point where retardation begins;" but, he adds, the "diminished density of the susceptible has to be taken into account," it "must have an effect in slowing the rate at which attacks proceed." The measles curve just defined sufficiently indicates that an epidemic may come to an end despite the existence of large numbers of susceptible persons in the population, merely on a "mechanical theory of numbers and density;" and that the assumption of loss of virulence or infecting power on the part of the organism is quite unnecessary.

In the light of the facts elicited concerning measles, some peculiarities in the behaviour of influenza become explicable; we can understand how, for example, in London, the spark is kept alight which later sets aflame a "trailing epidemic." Assume each case of influenza at the commencement of an epidemic capable of infecting, say, two fresh cases, and take the incubation period as one-third of a week, then in the first week, one, two, and four cases; in the second week, eight, sixteen, and thirty-two, will be attacked; and so on. As, however, larger numbers of those specially exposed (city men, theatre-goers, etc.), are stricken down, the rate of increase will necessarily slacken.

Suppose in the maximum week that the numbers attacked, approximately stated, are 240,000, 300,000, and 240,000. We may then interpolate for the weeks between the second and the maximum roughly as follows:—

Third	week,	64,	128,	250
Fourth	,,	500,	960,	1,800
Fifth	,,	3,200,	6,000,	11,000
Sixth	,,	18,000,	30,000,	50,000
Seventh	,,	80,000,	120,000,	180,000
Maximum,		240,000,	300,000,	240,000

In these six weeks upwards of 1,000,000 persons, or, say, 1 in 5 of the population, will have been attacked.

Now the outbreak will take much longer to decline to extinction than it took to rise, for those *specially exposed* have in large part been already attacked, and the disease must spread, in the main, among persons whose manner of life brings them comparatively little into contact with their fellows. The multiplier applied to each case has decreased from two to one in seven weeks, but it may take many months to diminish further to an equal extent—*i.e.*, to one-half. Thus the central figures of the second, third, etc., weeks are 2, 16, 128, 960, 6,200, 30,000, 120,000; each succeeding figure being derived from its predecessor by applying the multipliers 8, 8, 7.5, 6.25, 5, 4.3. We may continue this series of multipliers, stating them quite approximately somewhat as follows: 2.5, 0.5, 0.4, 0.36, 0.33, 0.30, 0.28, 0.27, 0.26, 0.25. The decrease, of course, becomes less and less rapid as time goes on. On this basis each crop of cases will still number over 100 up to the sixteenth week, and there will be an appreciable number of cases in each crop for some weeks later.

A further consideration must be borne in mind. New arrivals susceptible to influenza are continually entering London: there is, moreover, loss of insusceptibility on the part of some of those who have already been attacked. The rate of decrease of the multiplier will clearly slacken and slacken, and at length, after several months, may begin again to increase. We see, therefore, that, in London, influenza may well maintain an existence for years: as, indeed, it has done in our own time.

It is important to observe that the capacity for smouldering depends upon the existence of a large population densely aggregated. It may be roughly stated that, in London, with its 5,000,000 people, some million cases occur up to the time of maximum prevalence; there are, after thirteen weeks, some 5,000 cases a week; and a few cases still occur weekly even after six months. On this basis we see that, in a population of, say, 5,000 persons, the outbreak would have practically terminated after thirteen weeks, and be altogether extinct before the end of half a year. In such considerations we may find explanation of the behaviour of influenza in Martinique, Réunion, or the Fiji Islands.

The persistence of form of the London measles wave is not a little remarkable. Growth of population and alterations of its age, constitution, varying customs, and social conditions, have all left it almost undisturbed. Growth of population might at first sight, have been expected to exert

considerable influence. In island communities measles is introduced, prevails, dies out, and it may be many years before it again gains a hold; in Sweden, and in country districts of England, the disease presents "multiannual fluctuations;" in large towns it has assumed a biennial type. In London and New York we might expect greater frequency of recurrence still.

Then, again, fluctuations in the birth-rate might have been expected to have had more influence. Dr. B. A. Whitelegge has pointed out that there was "a distinct rise and fall in London measles mortality, with maxima in the early ''forties,' in the ''sixties,' and in the ''eighties,' over and above the biennial rhythm;" and he looked for evidence of altered quality of virus in this connection. In Sweden and Norway a rise in case-mortality accompanied each epidemic; there are no case-mortality figures for London, but Dr. Whitelegge turned to the more detailed records of certain provincial towns. The most striking of the instances he gives, that of Sunderland in 1885, is, it should be observed, an example of noteworthy change in the birth-rate.[1] A like variation, though a less marked one, occurred in Barnsley just prior to 1891. In a third instance (Hanley, 1888-89) it appears that school influence was operative.

Records of case-mortality in measles, when available, are apt to relate to special classes of population, and hence the influences exerted by age, social circumstances, etc., incessantly intrude. In the Norse epidemics, as Dr. Whitelegge has observed, the records relate to a few large towns and a number of country districts; it may be that varying degrees of prevalence in town and country, with accompanying age differences, account in some part for the alterations in case-mortality observed.[2]

[1] In the years 1880-84 the births were 5,065, 5,549, 5,913, 6,101, and 6,347. In London the range in the number of susceptibles has been found to be approximately from 120,000 to 180,000. In Sunderland, approximately one twenty-fifth the size of London, it would be from 4,800 to 7,200. An alteration in the number of yearly births from 5,000 to 6,300 would, therefore, obviously disturb the behaviour of measles very materially.

[2] Taking fourteen sparsely-populated districts in England and Wales, I found (*Transactions* of the Epidemiological Society, 1897) "during a period of forty years the deaths from measles, at ages 0-5, constituted only seventy-eight per cent. of the total deaths; whereas in London such deaths constituted between ninety-three and ninety-four per cent. of the total deaths." These different mortality rates represent, of course, still greater differences in prevalence at the higher as contrasted with the lower ages.

In differences in social circumstances, overcrowding, poverty, lack of proper tendance, etc., there is abundant scope for variations in case-mortality. Dr. Whitelegge says: "The case-mortality is greatly influenced by surroundings, the severity and fatality being greatest among the poor. The experience of epidemics amongst soldiers in time of war seems to confirm this." He adds a reference to the outbreak in Fiji in 1874, where "the case-mortality was enormous," but says, "not only neglect and exposure of the sick, but exceptional susceptibility of a population never before invaded by measles had to be taken into account. Whether," he adds, "the destructiveness of the pestilence was to be attributed entirely to this lowered resistance, or whether there was an increased intensity of the contagium —in other words, a true change of type—remains to be proved."

This outbreak, in which it is stated that some 40,000 natives succumbed to attack by measles, is one of the best-attested instances of its kind.[1] Mr. B. W. Corney wrote concerning it: "In considering the reasons why some epidemics of measles should have had a malignant type, great stress should, in my opinion, be laid on mistakes in dieting and therapeutic treatment." Again, he says: "Of the native population, those classes over whom adequate supervision could be exercised have suffered but slightly."[2]

Davis, writing of an epidemic in Samoa, computes that some 1,000 deaths occurred in a population of about 31,500, half of these being in adults. He considers that nine-tenths of the deaths could have been prevented had care been taken. It appears that the Tongans in this outbreak, "with the experience of Fiji," took some precautions, and thus the 15-30 per cent. case-mortality of Fiji was reduced to 4 or 5 per cent., and could have been further reduced. What becomes, then, of the special susceptibility of Polynesians?

This question of the attack of virgin communities needs clearing up. If there were such vulnerability, as is alleged, the evidence would be more conclusive. For the most part

[1] In an outbreak on the Amazon in 1749, whole tribes are said to have been cut off. Similar accounts are forthcoming from Hudson's Bay Territory, 1846; Astoria, 1829; the Cape (among Hottentots), 1852; and Tasmania, 1854 and 1861 (Hirsch). The Fiji Islands were attacked again in 1903; but the total mortality from "all causes" in that year is said to have been only 2,481.

[2] *Transactions* of the Epidemiological Society, vol. iii.

it relates to remote regions and long-past times, and unfavourable conditions — war, famine, neglect, etc.—have always played a prominent part. Hirsch, who strongly holds that "there are, generally speaking, no real differences to be made out in the course which measles runs at the various points of its large area of distribution," lays stress on the influence exerted by "mistakes in dieting and therapeutic treatment." He cites certain cases which, however, it is difficult to accept unreservedly: the 20 per cent. case-mortality of 1866 among Confederate troops; the 40 per cent. case-mortality in Paris (1870) in the Garde Mobile; that among French troops after the Italian war; and that in the Brazilio-Paraguayan war, when nearly one-fifth of the national army perished—"not from the severity of the disease," for 50 cases treated in private practice recovered, but from "want of shelter and proper food."

In the excitement of campaigning in bygone days, diagnosis may not have been precise. Certainly, the attack of large numbers of adults in a civilised country (30,000 Confederate troops) by measles excites suspicion.[1] However this may be, we have evidence near at hand of the malignity of measles under unhygienic conditions, and it would be easy to cite, not from the eighteenth century and from the Amazon, but from insanitary areas close at hand, case-mortalities of 15 per cent. Without going so far, then, as to deny alteration of quality in measles altogether, it may be noted as very remarkable, having in view the many circumstances which might be expected to bring about apparent change, that the constancy of type should be so marked. From the measles of 1670 (which, however, it must be admitted was selected for description by Sydenham as "the most perfect disease of this genus") down to the measles of to-day, in whatever part of the world observed, there is a wonderful fixity of character.

On passing now from measles to small-pox, we have to note qualifications. The possible occurrence of second attacks of small-pox cannot be ignored; moreover, it is necessary to take into consideration the disturbing influence of vaccination. It is clear that in pre-vaccination times—as, for example, in

[1] Typhus fever, septicæmia, etc., may have been in question. Bruce Low (*Transactions* of the Epidemiological Society, vol. xviii, p. 59) says: "Epidemic cerebro-spinal meningitis was widely spread during the Civil War, attacking the troops, specially the army of the Potomac, and in camp near Washington. It was severely felt among the negroes sent by the Confederates to Memphis."

Kilmarnock—the behaviour of small-pox, both as regards age-incidence and periodicity, closely approximated to that of measles at the present day. After vaccination was introduced, the inflammable material added year by year included not merely susceptible newcomers, for it becomes necessary to take account also of reversion to susceptibility on the part of persons vaccinated in infancy; moreover, as small-pox prevalence declined, the number of those protected by a previous attack of the disease diminished.

The conditions in large centres of populations resulted, as is generally recognised, in the production of short-period waves, such as those of London in the "'fifties" and "'sixties."[1] but these conditions cannot but have had influence in setting up long-period waves also, and the epidemics of 1837 and of 1871 may conceivably have thus resulted.

Dr. Whitelegge did not find conclusive evidence to show that "the minor epidemics which occurred in London at intervals of four or five years were attended with any temporary increase of severity." In 1871, however, he finds distinct suggestion of greater virulence and of increased power of epidemic diffusion, and he adds: "For several years previously there had been indications of increasing intensity in London—*i.e.*, a tendency to slightly greater destructiveness in each successive minor epidemic." Before accepting altered quality of virus as explanatory of the phenomena, there is need for recognising the difficulty of comparing the extent to which the several populations were protected. Further, conditions as regards treatment and isolation of cases have undergone material alteration, and it may be noted that practically nothing is known of the possibilities which Mr. W. H. Power's hypothesis of aerial convection opens up; it may be that the case-mortality of air-borne small-pox differs from that of other

[1] There can be no doubt that the continual influx into London of tramps from the country furnished the main supply of fuel for the flame. Dr. W. Black, writing in 1781, said: "Whatever share of small-pox mortality takes place in London amongst persons turned twenty years of age is almost solely confined to the new annual settlers or recruits who are necessary to repair the waste of London, and the majority of whom arrive in the capital from twenty to forty years of age." The London children, as the early years of the nineteenth century passed, were to an increasing extent protected by vaccination, but the supplies of new material from the country accumulated year by year, until at intervals of four or five years explosions became inevitable.

small-pox, and in any event differing modes of spread of the disease give opportunity for small-pox carried in one or another way to affect various classes of the population. Furthermore, in 1870-71, a great European war was in progress, and this country was again and again infected from France; it was to new arrivals from Paris, on the outbreak of hostilities, that the first exacerbation of small-pox in London was clearly traced, and the disturbed conditions in Western Europe in the year ensuing no doubt had influence upon small-pox mortality.

A striking contrast is presented in London by the 1901-02 small-pox case-mortalities of 34.6 and 10.3 per cent., and the 1903 small-pox with case-mortalities of 5 and 0.29 per cent. in unvaccinated and vaccinated respectively. But the fact needs to be borne in mind that 8,000 small-pox attacks and at least 1,000,000 vaccinations and re-vaccinations had served to augment resistance of the London population between the two outbreaks. It has been suggested that the 1901-02 small-pox came from France, and that it was more virulent than that of 1903, which came from America. Evidence as to this is not very precise; the earlier small-pox was undoubtedly, moreover, in numerous instances, so mild as to be confused with chicken-pox.

This question of resistance needs to be kept prominently in mind. Cambridge, hard hit in 1870-71, and then subsequently well vaccinated for many years, escaped quite lightly in the outbreak of 1903. McVail observes that second small-pox "is as a rule so much modified that it has given room for dispute as to what is and what is not small-pox." Stone-pox, water-pox, wind-pox, sheep-pox, swine-pox, horn-pox, and milk-pox were discussed by eighteenth-century writers. McVail concludes that "it may safely be asserted that these names nearly always mean modified small-pox, and that in the great majority of cases the modifying agency was a previous attack of the disease, either by infection or inoculation." He adds, however, that "a curious feature in connection with modified forms of small-pox is that they sometimes became so established in a locality and so fixed in type that they prevailed in epidemics." Scant justice has been done to environment in these matters; the range of case-mortality (according to Abbott's table, 0.5 to 12.5 in the vaccinated and 16.1 to 60 in the unvaccinated) is commonly attributed to altered virus, while the age of those attacked, interval

between epidemics, and numerous other obviously important considerations are apt to be lost sight of. In some of the very low case-mortalities (*e.g.*, that of 0.2 recorded by Vogt from Edinburgh) chicken-pox may, as Simon pointed out, have been in question. Again, the fact that case-mortality in small-pox is particularly low in children over two years of age (and this has always been so, as the Aynho figures indicate) explains a good deal of supposed alteration of virulence. Possibly cases are now included which would have been left out of count in days gone by; some of those notified in the London outbreak of 1901-02 presented only some half dozen or dozen pustules; these were met with in persons protected by previous vaccination—may not similar cases have occurred in persons protected by previous small-pox in the eighteenth century? Again, so much turns upon the date and quality of vaccination, and it is important also that inquiry should be made as to previous attack by small-pox. This last-named question has special interest in connection with the reported mild small-pox of South Africa (Kaffir "Amaas"), India (Punjab), West Indies, Trinidad, etc. From a report my colleague, Mr. W. McC. Wanklyn, has shown me, I gather that the Trinidad small-pox occurred, for the most part, in persons who had either been vaccinated or had previously suffered from small-pox. The broad fact remains that only when the field of view is contracted are anomalous forms of the disease encountered; on a comprehensive survey, and when due regard is given to environment and to degree of protection, artificial or natural, small-pox remains remarkably constant in type.

On turning to variations in quality exhibited in scarlet fever and diphtheria, a preliminary difficulty is the apparent intermingling of the two diseases. There are instances of simultaneous appearance of the two clinical types in the same epidemic, and even in members of the same family. Both diseases are milk-borne, and the intermingling referred to is especially met with in milk outbreaks. There is the parallelism in behaviour as regards "school influence" and "return-case" phenomena; and again there is the relation of both diseases to meteorological conditions, and especially to years of drought. The interlacing of the features regarded as typical, of scarlet fever on the one hand and diphtheria on the other, in eighteenth and early nineteenth century literature, finds its counterpart in the confusion of nomenclature which has existed within the period of

registration of deaths. Finally, suspicion has been entertained as to bacteriological relationships.[1]

Whether we elect to continue to speak of two closely related diseases, scarlet fever and diphtheria, or of one throat malady, the records yield, as has been seen, clear evidence of long—approximately 30-year—oscillations, with minor waves of three or four years' period. Are these the result of change in the organism, or in the host and the environment generally?

Dr. Whitelegge cites case-mortality figures as proof of severity of type at times of increased prevalence. The figures are, however, open to interpretation in other ways. The London Fever Hospital statistics show, for example, that at ages 0-5 the case-mortality varied not in direct but in inverse correspondence with variations of prevalence; and it is well known that remarkable changes in the age-distribution of patients admitted to that hospital have occurred at epidemic times.[2]

While urging caution in this matter, there can be no question as to the altering character of the disease in the 30-year periods; and if this be admitted, it may be argued that it is idle to deny the like possibility in the short-period waves. The point at issue is: Do the changes connote alteration of the virus, or merely in the effect produced in the soil? The two diseases faithfully fulfil their periodic times, when a particular population is being kept under observation; now they are in "non-virulent" phase; in fifteen or twenty years' time they may be again in "virulent phase."[3] But the organism may be in one phase in one population and contemporaneously in the other phase in a neighbouring population; for it is an everyday observation that an epidemic losing intensity in one place may in spreading elsewhere show unabated energy. Surely, then, the supposed changes in virulence are really changes in reaction between a parasite and more or less immune hosts; the phenomena of immunity of individuals and of populations after attack clearly suggest this.

[1] See various papers in *Transactions* of the Epidemiological Society—by Dr. Ransome, 1875; Dr. Franklin Parsons, 1883-84; and Dr. J. T. C. Nash, March, 1906. See also Paper by Dr. Biss (*Lancet*, November 7th, 1903), and *Reports* to Local Government Board by Dr. M. H. Gordon.

[2] Notable alterations of age-incidence, moreover, accompany the waves of prevalence (*Transactions* of the Epidemiological Society, 1897).

[3] Gottstein explains the altering age-incidence of diphtheria in Germany as being caused by such variations in the soil.

A word of explanation is, perhaps, here necessary. Altered reaction between host and parasite means alteration in the host. Why not also in the parasite? The virulence of an organism is enhanced and attenuated under laboratory conditions by passage through susceptible and insusceptible animals; can it be supposed, therefore, that the sore-throat organism of a community tested in the trough of a wave of multi-annual prevalence would prove identical with one taken at the crest of the wave? The organism possibly undergoes change, but it must be insignificant in comparison with the epiphenomenal change in the reaction between parasite and host. The fact which stands out as specially remarkable is that this reaction comes back again and again to the point of departure; so that when a long period is passed in review there are cycles upon cycles, it may be, of epiphenomenal variation, but little or no evidence of evolutionary change in the disease organism itself.[1] For examples of the latter we must turn, not to seasonal fluctuations, short-period waves, or even multi-annual fluctuations or nutations, but to *secular* nutations; and even then the evidence, as has been seen, is singularly unconvincing.[2] Indeed, in the absence of such evidence, we feel that

[1] It is comparatively easy to deal with species at first hand, but most difficult to deduce the fixity or variability of a species from observing effects produced by it. Thus Weismann examines instances which "prove that an immigrant species can spread over a new area without immediately varying" (*e.g.*, the sparrow in the United States and the evening primrose in Europe). But consider such a case as that of the introduction of goats into St. Helena. The young trees were devoured as they grew, and with extinction of the forests the indigenous insects and birds of the island were doomed to destruction. It would be absurd, however, to deduce from a changed St. Helena a change of type in the invading goat. Again, Weismann refers to the effect of the introduction of rabbits into Kerguelen land in 1874. The Kerguelen cabbage (Pringlea antiscorbutica), which flourished on the island in 1840, was found, in 1898, to be growing only "upon perpendicular cliffs, or upon the islands lying out in the fiords." The face of the island was transformed, but there is no evidence that the rabbit had undergone change of type.

[2] The altered behaviour of plague, typhus, malaria, and dysentery in this country to which Davidson, for example, alludes, may well be attributed to change of environment. He speaks of "new diseases"—his first example, sweating sickness, has been discussed in Lecture I., and dengue and cerebro-spinal meningitis should be regarded as newly-described diseases rather than new diseases. His instances of extinction or modification of diseases are far from being convincing, and his allusion to the temporary assumption of epidemic character by syphilis and leprosy counts for but little, so meagre is our knowledge concerning the alleged phenomena.

it is not an explanation of change, but of persistency of type that is needed. For this we may fall back either upon the phenomena of variation under domestication or under conditions of isolation, with reversion to ancestral characters as soon as free crossing with allied forms comes into play; or, to take another and more promising analogy, we may instance the masterpieces of the florist produced by grafting or layering, variety following upon variety; and may wonder whether the germs of disease, which multiply asexually in the human body, may not have sexual developmental phases by which the continuity of the species is preserved.[1]

I have considered now possible explanations of persistency of type, and have suggested that in the unstable diseases apparent change of type may result from interplay between the organism and its environment.

Some further considerations having important bearing upon the question of the origin of disease species remain to be alluded to. Must we assume that small-pox and chicken-pox, measles and German measles, have branched off from a common ancestral stock, just as the different species of hæmamœba, spirochæte, trypanosome, and bacterium have done? Again, where is the line between species and species to be drawn? In dealing with bacteria, for example, are differences in colour reaction, in power of fermenting various sugars, clotting milk, liquefying gelatine, and killing animals, to be necessarily regarded as having specific value?[2] This question assumes an acute form when agglutination tests come under consideration, for on

[1] This brings us to some such conception as was put forward in Mr. W. H. Power's cholera hypothesis of 1883, a hypothesis which at once serves to explain certain phenomena to which he refers, and also to reconcile extreme variations of virulence of the cholera organism, in particular areas and at particular times, with stability of cholera as an endemic and epidemic disease. It is a curious fact that the two water-borne diseases *par excellence*, enteric fever and cholera, have been found to be communicated by shell-fish and fish. The limitation of cholera, in recent European experience, to river populations, and the extraordinary way in which, in 1832, it attacked fishing populations in this country and in Scotland (see Creighton's *History of Epidemics*), may be considered in relation with the fact that in its endemic area it affects a population to a large extent living in boats, and feeding upon what can be caught in the rivers.

[2] See paper by Sims Woodhead (*Transactions*, Epidemiological Society, 1890-91), and paper by A. D. Hall (British Association Meeting, 1905), and again, "Observations on Influence of Symbiosis on Virulence," by Klein, in *Thirty-third Annual Report of Medical Officer of Local Government Board*,

application of these the bewildered observer in the field finds that of two cases exposed alike to infection, one is taken by the bacteriologist and the other left.[1]

There is, perhaps, no family of disease organisms which presents more instructive phenomena for study of the criteria used for the differentiation of species than the colon group. At the one extreme stands the bacillus coli (Escherich) and its relations, at the other end the bacillus typhosus and its various "strains," and intermediate between them there are organisms such as those of dysentery, hog-cholera, paratyphoid fever, and the many bacilli associated with meat-poisoning.[2]

[1] There are signs of rebellion in the bacteriological camp itself. Thus, Lieutenant F. P. Mackie (the *Lancet*, September 23rd, 1905, p. 874) quotes authority for the statement that maximum agglutination value may be given by typhoid serum "with bacilli which were shown to have no ætiological relation to the disease; and further, that the specific agglutination value is not invariably above that of the group agglutination, which indeed cuts at the root of the *rationale* of the differentiation of paratyphoid and enteric fevers." Lieutenant Mackie boldly adopts the view that auto-intoxication by bacillus coli communis, under certain unknown conditions of lowered bodily resistance, culminating in what amounts to transmutation of a saprophyte into a parasite, "explains the whole question." He even speculates on the "resemblance between enteric fever, paratyphoid fever, and dysentery, and the affinities between the Eberth-Gaffky bacillus, the coli communis bacillus, and Shiga's bacillus of dysentery." "It might be shown," he says, "that there is a suggestive gradation between the types, not only in their clinical manifestations, the site and type of the intestinal ulceration, and the degree of septicity of the fever, and so on, but more markedly in the biological gradation from the bacillus at one end of the arc to that at the other end." See also "Paratyphoid and Typhoid Fever," by A. E. Boycott, *Journal of Hygiene*, January 1906, especially p. 52, as to "irregularity of agglutination results," and the observations of F. W. Andrewes in his recent Report on sewer air as to the alleged value of chemical tests.

[2] The group, according to Trautmann, may, by applying agglutination tests, be divided into five sub-groups. H. de R. Morgan (*British Medical Journal*, June 10, 1905) also gives a detailed classification. He describes an "enteritidis sub-group," which includes Gaertner's bacillus, the closely-allied bacilli isolated in the meat-poisoning outbreaks of Aertryck, Moorsele, Haustedt, and Breslau, the bacillus morbificans bovis, the bacilli of Günther, Abel, and Rumfleth, the bacillus typhimurium, the bacillus psittacosis, and two varieties of hog-cholera bacilli; closely approximating to these are other sub-groups, containing the paratyphoid bacilli, the food-poisoning bacilli (Wesenberg, Grünthal and Friedeberg) the hog-cholera bacillus (McFadyean), and bacillus pseudotuberculosus; only a little further removed stand bacillus coli, bacillus acidi lactici, bacillus lactis aerogenes, bacillus cloacæ, bacillus pyogenes fœtidus, and the typhoid and dysentery bacilli. See also recent papers by Zupnik, *Zeit. für Hygiene*.

It is held that certain peculiarities differentiate these closely-allied organisms into distinct species, and in default of other criteria reliance is placed upon the agglutination test. The serum from a particular meat-poisoning outbreak clumps its special bacillus in higher dilutions than other meat-poisoning bacilli; a new designation, *paratyphoid*, is needed to describe a form of disease distinct from typhoid fever; it is also held that there are particular strains or races of typhoid bacilli. On culture media the same story is told; thus, to take one instance only—viz., the breaking-up of certain sugars—the typical bacillus coli (Escherich) ferments lactose, but not cane sugar. Given a bacillus which resembles it in all other particulars, but which does not ferment lactose, or does so only feebly, or which ferments cane sugar, or presents some suggestion that it is capable of doing so in a slight degree, is such an organism to be regarded as bacillus coli (Escherich) or as a distinct species? Again, there are said to be immune bodies in number untold, each specific for its particular toxin. The phenomena of bacteriolysis, hæmolysis, and the rest, all need for their explanation these specific "go-betweens;" indeed, according to some authorities, the ferments, or "complements," which the "go-betweens" annex are also specific. There have not been lacking dissentients who have found it hard to people the blood and tissues, even in imagination, with such myriads of specific bodies.

As evidence of the need that has been felt for buttressing the specificity thesis, it may be noted that the attempt has been made to put the matter to a sort of test by showing that no change from one species to another has occurred under laboratory conditions. Klein has recovered bacillus coli unchanged from tap-water after many days or weeks. MacConkey found it retained all its characters unaltered after an exposure of 358 days to what was a changing and unfavourable environment: a result distinctly opposed, as he puts it, "to the idea that this bacillus ever becomes atypical." But we need, in connection with employment of the fermentation and other tests relied upon, to remember, as Sir William J. Collins has pointed out, that "the possibilities of environment are not exhausted by the confectionery of the laboratory." We need, too, to keep in mind the caution hinted at in Sheridan's *Critic*, that inability to see the Spanish fleet may be fully explained by the fact that "it is not yet in sight." A recent observation made

by Dr. M. H. Gordon is very interesting in this connection. He worked out "nine reaction tests" for the differentiation of streptococci, and then endeavoured to ascertain how far the organisms, behaving in a particular manner, continued to do so after being passed through mice. Nine of eleven streptococci remained unaltered, but in two instances an alteration had taken place. "One streptococcus had gained positive reaction for salicin, the other had lost its positive reaction for neutral red."

The question as to the specific character of allied forms of bacilli, immune bodies, etc., will no doubt receive a good deal of further attention. Certain considerations bearing on the subject may be here referred to.

In the case of allied forms of bacilli, distinguished one from another by their varying behaviour as "polysaccharide fractors," it becomes necessary to regard each bacillus as having attached to it "enzymes" capable of fermenting the several sugars in question. Reasoning from the analogy of small-pox and vaccinia (which have been quite abruptly converted the one into the other), is it not conceivable that as a result of development under certain conditions (and these not necessarily laboratory conditions) a bacillus may lose an enzyme of one sort, or become associated with one of another sort, thus being converted into a changed organism from a sugar-fermenting point of view? On such view of the matter it may also prove to be very difficult or even impossible to imitate in the laboratory the conditions necessary for displacement of the enzyme, and a negative experiment, such as that with tap-water and bacillus coli may be of minimal value.[1]

The conception of the bacillus as a kind of host with attached "enzymes" affords, it may now further be noted, a possible clue to the difficulties arising in connection with immune bodies, agglutinins and the like. Take first the simple case—an organism with a single attached "enzyme."

[1] This may perhaps be made more clear by replacing in thought the bacillus by a man and its "enzyme" by a tapeworm. Suppose, then, that question arose as to whether a man harbouring tænia mediocanellata and another man harbouring tænia solium, belonged to the same species. It would scarcely elucidate the matter were some inquirer to cause the first man to drink tap-water for 358 days, and then demonstrate that his parasite exhibited the characters of tænia mediocanellata and not those of tænia solium. The result would not dispose of the question as to whether the first man could be infected with tænia solium or the second with tænia mediocanellata. Neither does the tap-water experiment dispose of the possibility that one "enzyme" may replace another in the bacterium.

Introduction into a favourable medium is followed by rapid multiplication, which is by-and-by checked, as products of fermentation accumulate, and finally ceases; we may regard the enzyme if we choose as in a condition of equilibrium, influenced equally, but in opposed directions, by two "mass actions"—that exerted by the fermentable substance, and that exerted by the fermentation products.[1] Similarly, in the analogous highly complex immunisation process a point of equilibrium is, it may be, reached when nutrient materials and excretory products (toxins, etc.) exert equal but opposite "mass-actions."

We may, indeed, here find explanation of the aggregation of bacilli in "clumps," for it may be suggested that when the "enzymes" cease to act on the external medium they operate on the germs themselves. A phase which we may perhaps style a "resting form" of the organism may be thus produced, and this "resting form" may constitute a centre of attraction for bacilli. Just as when silk is rubbed upon glass the one is charged with positive the other with negative electricity, so the development of "resting forms" may engender chargings of opposite sign on the resting forms themselves, and on the bacilli; and there may thus result groupings of bacilli about the centres of attraction constituted by the presumably ultra-microscopic resting forms.

Thus far for agglutination in the simple case; but now, suppose the bacillus to act as host for multiple "enzymes," each of which may operate upon the blood and tissues of the host. Many fermentations now occur, and the "mass-action-equilibrium points" will be reached, some earlier some later, the blood and tissues "fermenting clear" for enzyme after enzyme, until the last has completed its work. Do the "resting forms" only begin to appear under such

[1] That there is justification for such a view of the matter will be seen on reference to certain phenomena in fermentation and agglutination processes. Yeast fermentation proceeds until there comes a time when "the resulting alcohol is injurious to further action" (Newman) on the part of the yeast. Charrin and Roger, in 1889, found that "when the bacillus pyocyaneus was grown in the serum of an animal immunised against this organism, the growth formed a deposit at the foot of the vessel, whereas a growth in normal serum produced a uniform turbidity." Again, Grüber and Durham, in investigating Pfeiffer's reaction "found that when a small quantity of the serum of an animal highly immunised against a particular motile organism (cholera vibrio, typhoid bacillus, etc.) is added to an emulsion of the organisms, the latter lose their motility and become agglutinated into clumps" (Muir and Ritchie's *Manual of Bacteriology*).

conditions when equilibrium is finally attained, or do they gradually accumulate from the moment when the first enzyme has ceased to operate? There is here the semblance of a clue for threading the mazes of agglutination phenomena.

Why should not two "meat-poisoning bacilli," for example, while closely approximating to each other in almost all respects, present slight differences as regards their attached enzymes? These differences might find expression, upon inoculation of bacillus A and bacillus B respectively, in the development of differing agglutinating properties of sera of the immunised animals. A serum which has reached "mass-action-equilibrium point" for bacillus A has presumably not yet attained to that point for bacillus B, and therefore serum A will not clump bacillus B in the high dilutions at which it clumps bacillus A; but serum A may, in so far as the properties which are here all important are concerned, approximate closely enough to serum B to clump bacillus B in moderate dilutions, and may have clumping capacity for bacillus B distinctly greater than it has for, say, bacillus typhosus. In some such tentative hypothesis as this may be found explanation of the "specific" relationship between serum and bacillus. Again, from such a point of view as this, the otherwise mysterious play of chance which repeatedly associates together the typhoid and paratyphoid bacilli becomes explicable. Gaehtgens (*Centralblatt für Bacteriologie*, March 10th, 1906) has collected a number of instances in which bacillus typhosus and bacillus paratyphosus have been found simultaneously, or after an interval of a few days or weeks, in material obtained from one and the same individual. The fact that of the small number of persons hitherto demonstrated to harbour paratyphoid bacilli, quite a considerable percentage also harboured bacillus typhosus, seems to call for explanation, and this an hypothesis such as that just formulated readily affords. Boycott has recently made some observations (*Journal of Hygiene*, January, 1906) on coincidence of the two organisms.

Whether this method of looking at specific agglutination phenomena be regarded as possessing interest or not, there remains the possibility that, in connection with the attainment to "mass-action-equilibrium point," an as yet unrecognised phase of parasitic existence may be evolved. In this unknown phase the organism may or may not fix stains, pass through filters, withstand a temperature of

70° C.—there is no reason for assuming it will comport itself as does the familiar bacillus in the respects named.[1]

This digression has been necessary in order to "clear the air" with regard to the question of specificity. If orthodox doctrine be accepted, the name of distinct species in the colon group is legion, and the stability of each, so far as the individual bacteriologist is concerned, practically unassailable. On the other hand, if it be assumed that a particular colon bacillus may live and develope "symbiotically," so to speak, with one or more enzymes, which under certain conditions may be replaced by others, we then clearly have to hand, in the permutations and combinations of a limited number of enzymes, scope for comprehending in conception a very large number of nearly-related organisms. If it should be possible thus to reduce, for example, the whole meat-poisoning tribe to two or three bacilli, in varied association with some half dozen enzymes, the simplification introduced would be great; and it would at least be no longer necessary to crowd the blood and tissues with standing armies of specific bodies.

It may, perhaps, be said that whether we postulate on the one hand 100,000 species of bacillus coli and its allies, or on the other quite a limited number of species having in varied combination some five or six associated "enzymes," the difference is fundamentally one of terminology only. Yet this is not so. From the latter point of view, our conceptions with regard to certain phenomena in the life-history of the organism are greatly simplified, while at the same time the bacillus, considered from an evolutionary standpoint, is endowed with a stability far transcending that which it possesses on the former hypothesis. The assumption that fermenting property can suddenly be

[1] The hypothesis that some such unknown phase exists may serve to explain certain phenomena which have been observed, such, for example, as the infectivity of milk in which the tubercle bacillus cannot be demonstrated by microscopical examination; or again, the results obtained by Houston with regard to the virulence on inoculation in guinea-pigs "of broth cultures incubated with minute amounts of human fæces, while broth cultures of bacillus coli isolated from parallel amounts of the same material were commonly either non-pathogenic, or at all events not virulent." A possible misconception with regard to the suggestions made above may be guarded against. The hypothesis put forward is not to the effect that the bacilli are necessarily all made to yield the unknown phase at one point of time, the moment of attainment of "mass-action-equilibrium." The conception would rather be that the tendency to development of the unknown phase is at its maximum, and that certain bacilli readily pass into it then, though others may still be obdurate in this respect.

gained runs counter, it is true, to current teaching. The bacteriologist has to admit that such powers may be lost—this is an everyday laboratory experience—but he is reluctant to agree that they may be newly acquired. A doctrine which carries with it some limitation upon the present-day demands of the founders of new bacteriological species at least possesses this in its favour: that it furnishes a simple explanation of the behaviour of epidemics, as ascertained from records of disease.

The bacteriologist who claims that the most minute differences are inseparably connected with and distinguish species of bacilli throughout long ages, must reckon with the fact that the more numerous the species, the greater must have been the ability to vary from an original stock —the whole question is, indeed, not one as to ability to vary, but as to the number of stable forms and the distances which separate positions of equilibrium one from another.

Much that has been said of varieties of bacillus coli holds good of streptococci. Furthermore, just as various *strains* of these organisms may be assumed to be converted, at a stroke, one into another by a change of "enzyme," so it may be that supposed specific forms stand in a like close relationship. The doctrine may find application, for example, in connection with tubercle bacilli of bovine and human origin; or, going still further afield, some difference, in the parasites associated with a parasite, may be expected to yield explanation of the association between small-pox and vaccinia, scarlet fever and diphtheria, dengue and influenza, enteric fever and dysentery, or typhus and relapsing fever. We may even conjecture that immunity, in some instances, may mean that the parasite has been harnessed to some other parasite or enzyme which robs it of its former virulence. Here, of course, we must not lose sight of the fact that the particular organism the bacteriologist has drawn attention to may itself be a mere sub-parasite, capable of living symbiotically with the parasite in chief. Thus the influenza organism may at one time live in association with Pfeiffer's bacillus, at another with the micrococcus catarrhalis, and so on; or the throat distemper organism may be yoked now with the diphtheria bacillus and now with the streptococcus conglomeratus.

A particular organism may conceivably cause more than one disease in man by being introduced by different intermediary hosts; and again, distinct diseases may result when the parasitic organism is accompanied by different enzymes or sub-parasites temporarily associated with it.

With regard to the former suggestion, it must be borne in mind, however, that only particular species of Anopheles can communicate malaria, nearly allied forms being unable to do so; and thus the organism, which only possesses power to develop in a strictly limited number of species of insect hosts, stands in marked contrast to the anthrax or the tubercle bacillus, with their ability to affect animals of widely differing species; it may be that in species in which the sexual phase of development is thus restricted the mere asexual cycle can be completed in numerous hosts. The second suggestion may be further considered from various points of view. Thus there is the fact, if it be one, that protection may be renewed and maintained by repeated exposures. The nurse and medical man conceivably owe immunity to their ability to attach to invading organisms some enzyme which renders development in the human body a cause, not of disease, but of renewal of protection against disease. Again, the occurrence of mild cases of typhus fever, or of dengue or influenza (during inter-epidemic periods) readily fits in with an hypothesis of association of the dominating organism of the disease with some attenuating sub-parasite. Just as chemical atoms combine to form molecules and molecules to form compounds, so may sub-parasites be combined with parasites, and these again with higher parasites. Dean Swift, after pointing out that Hobbes has proved "every creature lives in a state of war by nature," goes on to relate how naturalists—

> "Observe a flea
> Has smaller fleas than on him prey;
> And these have smaller still to bite 'em;
> And so proceed *ad infinitum*."

In modern bacteriological theories of disease we may have concentrated attention too exclusively upon particular links in the chain of parasitism—in other words, we have studied the parasites which develop under laboratory conditions and have held disease to be bound up with them, forgetting that a particular parasite may be merely one of a series, and that it may in some cases be replaced in that series by another parasite, and then for the time being, and under the local conditions in question, cease to have any concern with disease at all. The records of epidemics suggest that some such explanation must be looked for, to reconcile the extraordinary persistency of disease types with the no less remarkable variability of the organisms to which the bacteriologist attaches importance as causes of disease.